# T/NK-cell Lymphomas

## Including Primary Cutaneous Subtypes

**Christina Poh, MD**

**Assistant Professor of Medicine**

**University of Washington**

**Fred Hutchinson Cancer Center**

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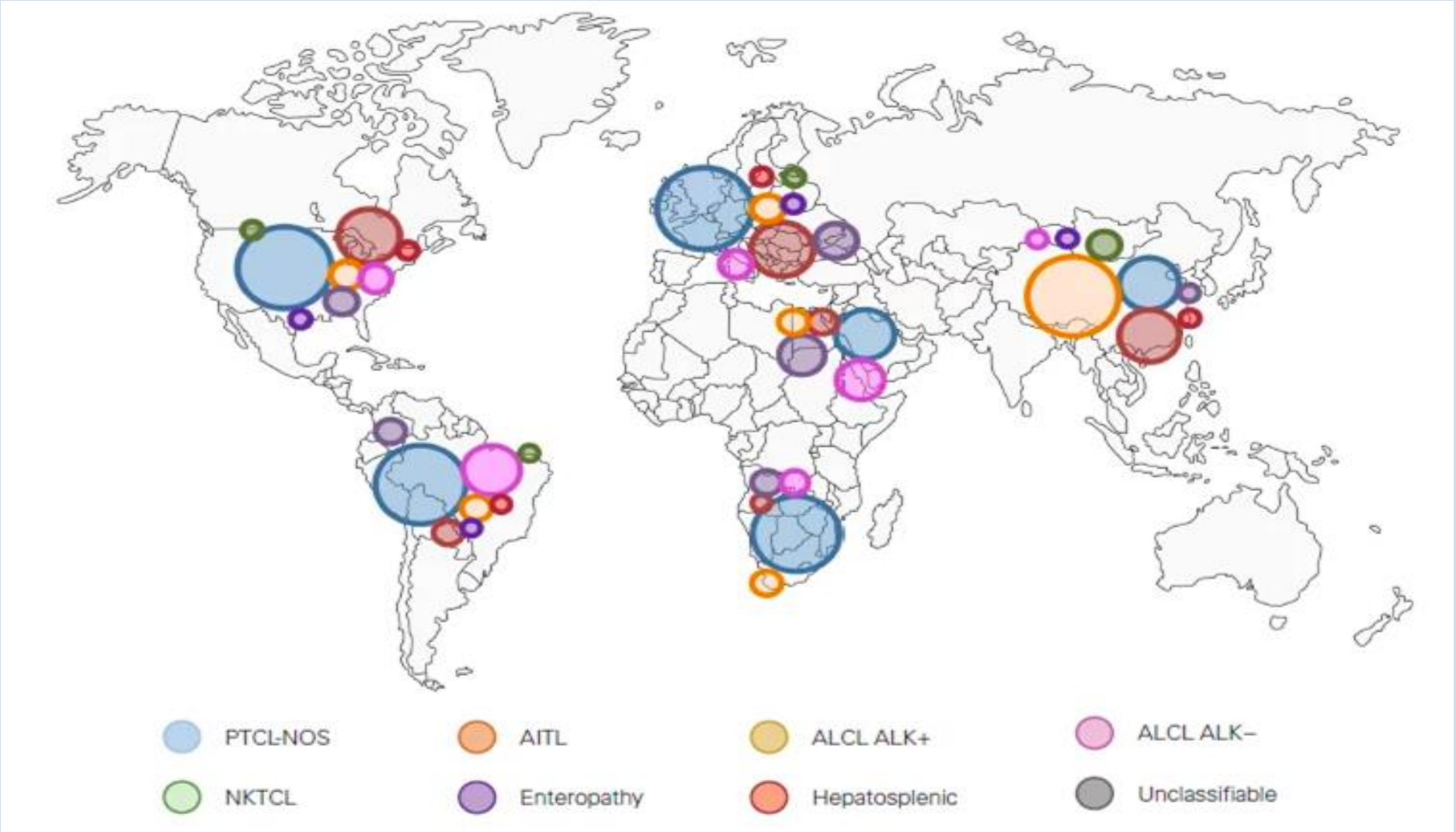
# COI Disclosure

- Research Funding: Incyte, Dren Bio, Pfizer
- Consultancy: Acrotech, Seagen, Ipsen

# T/NK-cell NHL Landscape

- Epidemiology
- Peripheral T-cell lymphomas
  - Front-line management
  - Relapsed and refractory management
- Other T/NK-cell malignancies
- Cutaneous T-cell lymphomas

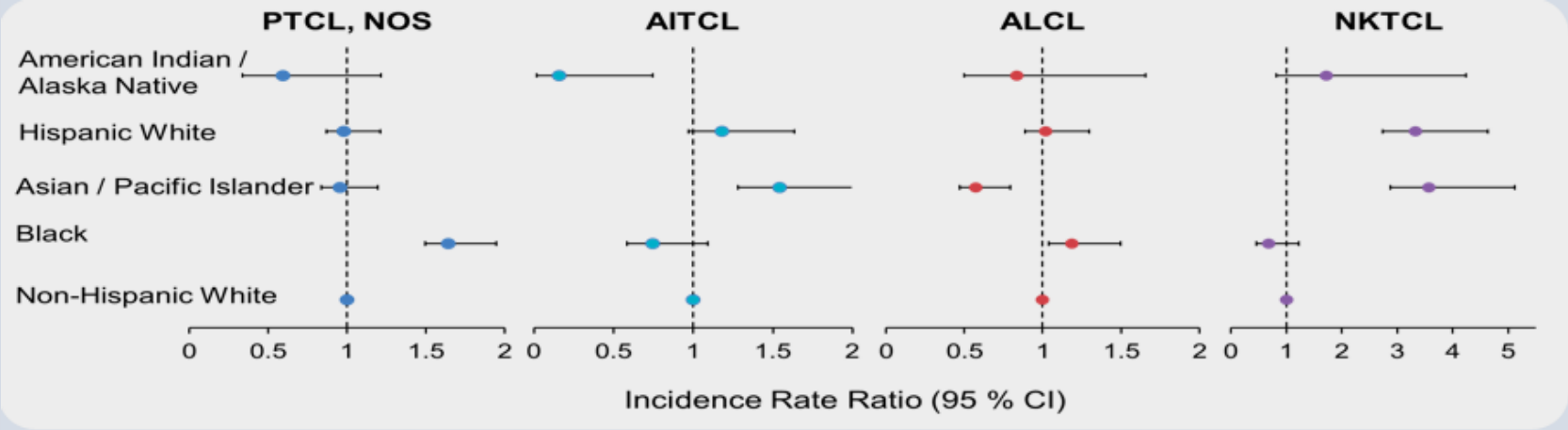
# T/NK-cell NHL: Global Epidemiology




*Zing et al. Oncology 2018*

# T/NK-cell NHL: US Epidemiology

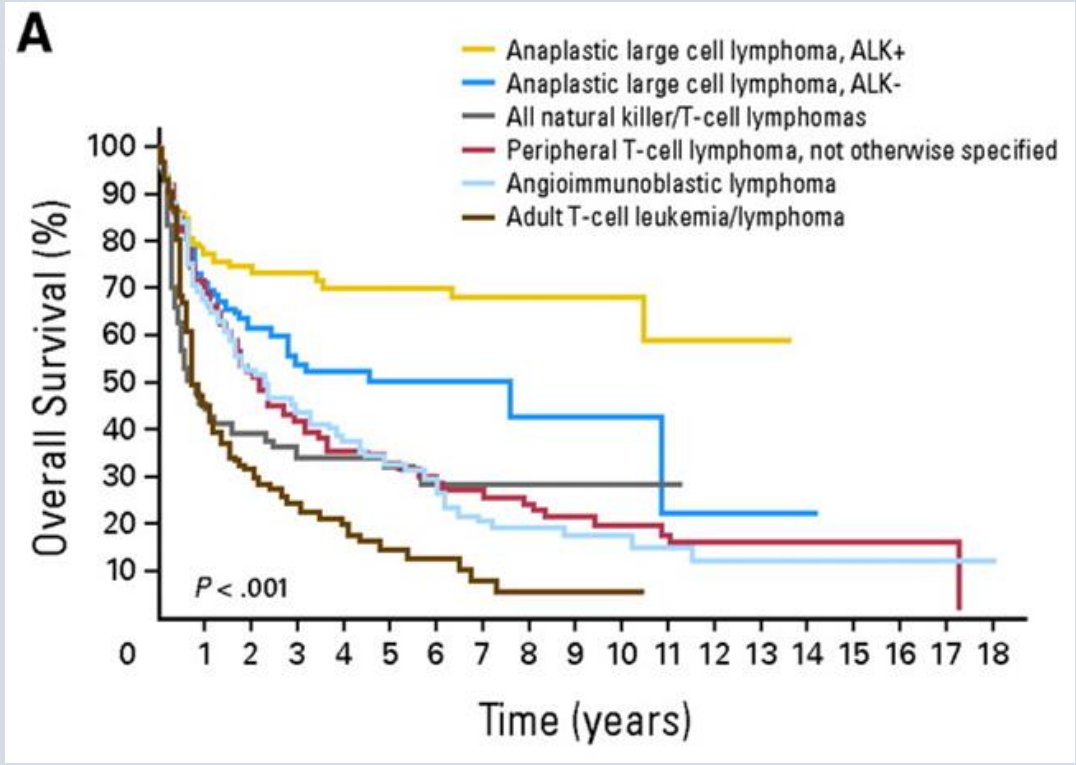
| Registry | PTCL-NOS | AITL | ALCL, ALK+ | ALCL, ALK- | NK/TCL | ATLL |
|---|---|---|---|---|---|---|
| BCCA | 59% | 5% | 6% | 9% | 9% | NR |
| COMPLETE | 34% | 15% | 11% | 8% | 6% | 2% |
| IPTCL (NA) | 34% | 16% | 16% | 8% | 5% | 2% |




*Vose et al. JCO 2008*
*Savage et al. Ann Oncol 2004*
*Foss et al. Blood 2012*
*Adams et al. JCO 2016*

# Peripheral T-cell Lymphomas

- Heterogeneous group of predominantly nodal lymphoproliferative disorders derived from mature T-cells
- Accounts for 10-15% of all NHL cases
- Generally aggressive clinical course
  - Poor outcomes with standard therapies (5-year OS of <30%) with the exception of ALCL

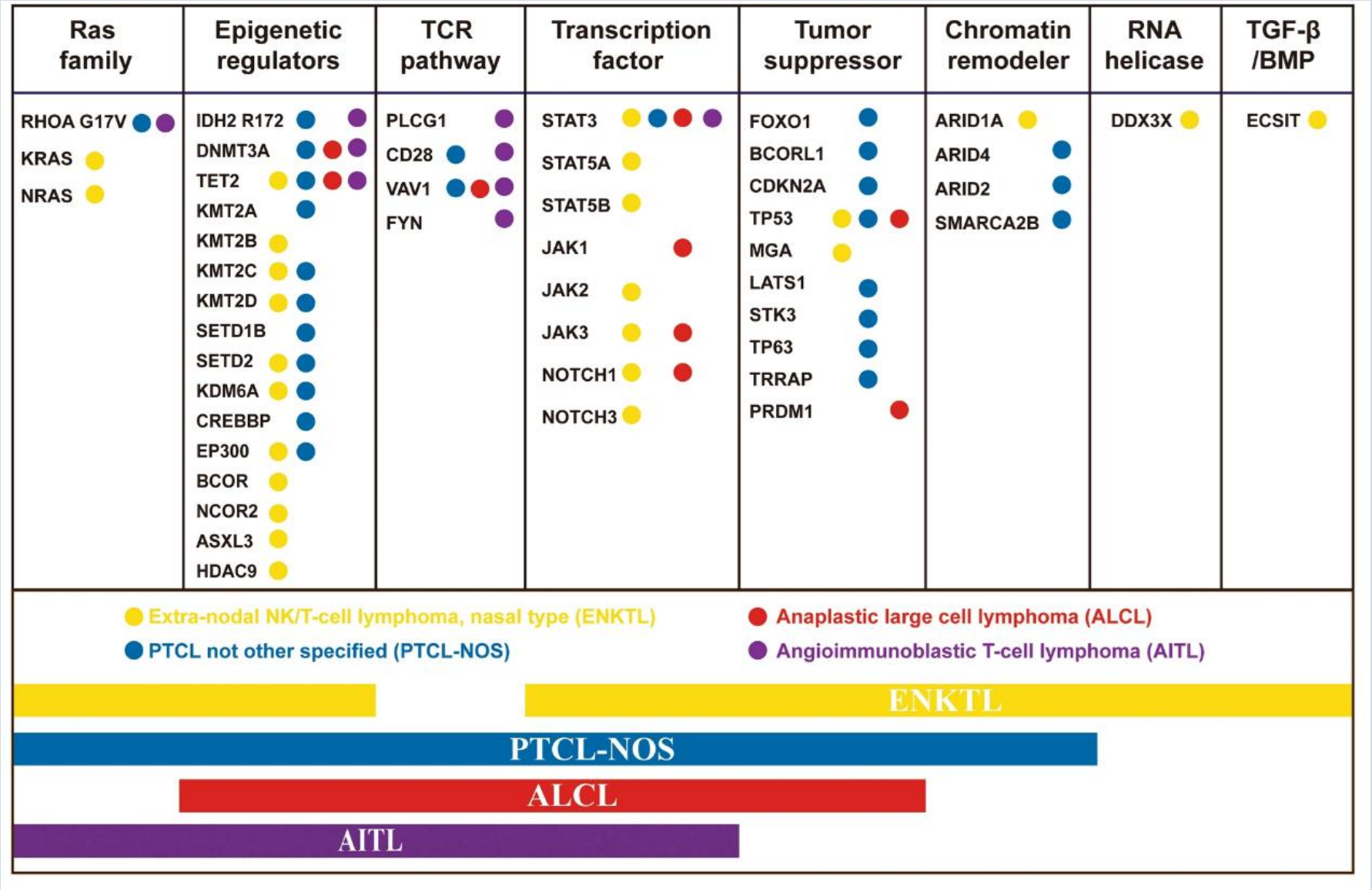



*Vose et al. JCO 2008*

# Clinical Prognostic Models in PTCL

| Clinical Variables | IPI | PIT | PIAI | KPI |
|---|---|---|---|---|
| Age | X | X | X | |
| Stage | X | | | X |
| LDH | X | X | | X |
| ECOG PS | X | X | X | |
| X-nodal sites | X | | X | |
| BM involvement | | X | | |
| Platelet count | | | X | |
| B-symptoms | | | X | X |
| Regional LN+ | | | | X |

# Molecular insights into PTCL



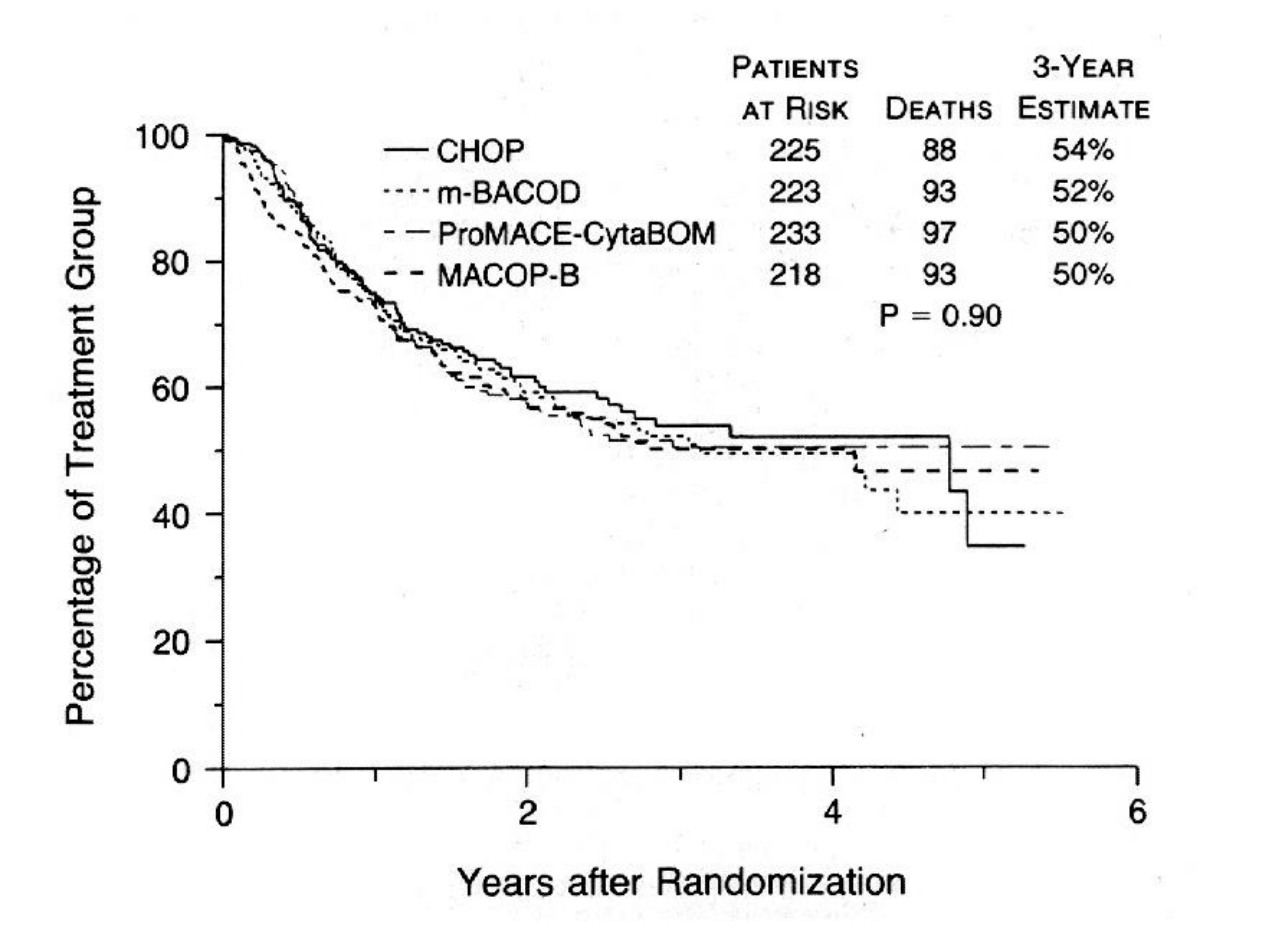

*Xie et al. Exp Hematol Oncol 2020*

# Molecular Analysis in PTCL

| Gene | Testing Indication | Implication |
|---|---|---|
| ALK | ALCL | associated with a favorable prognosis<br>***t(2;5)*** *translocation involving ALK and NPM* |
| DUSP22-IRF4 | ALK- ALCL | associated with similar prognosis to ALK+ disease |
| TP63 | ALK- ALCL | associated with aggressive disease course |
| TET2 | PTCL/AITL | aids with AITL diagnosis and guides R/R treatment |
| IDH1/2 | PTCL/AITL | aids with AITL diagnosis and guides R/R treatment |
| RHOA | PTCL/AITL | aids with AITL diagnosis and guides R/R treatment |
| DNMT3A | PTCL/AITL | aids with AITL diagnosis and guides R/R treatment |
| TBX21 | PTCL-NOS | Associated with a favorable prognosis |
| GATA3 | PTCL-NOS | Associated with an unfavorable prognosis |

*Horwitz et al. J NCCN 2022*

# Upfront Treatment: CHOP

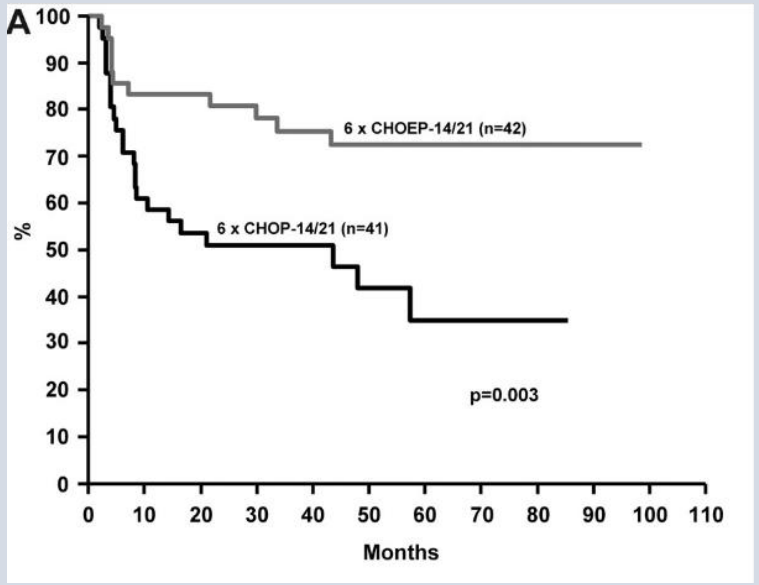



| NHL Subtypes | |
|---|---|
| Follicular large cell | Diffuse large cell |
| Diffuse small cleaved cell | Large cell immunoblastic |
| Diffuse mixed and small and large cell | Small non-cleaved cell (Burkitt and non-Burkitt type) |

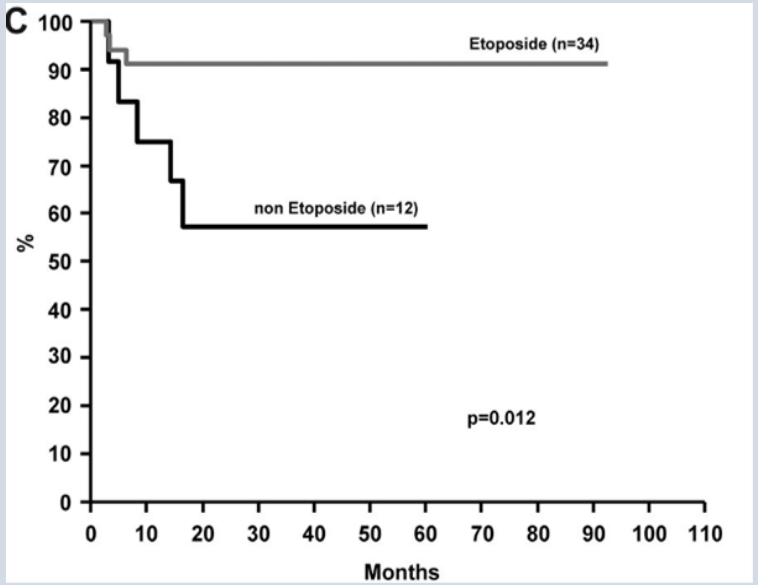
- CHOP standard of care by default
- 25% of PTCL patients are primary refractory to CHOP

*Fisher et al. NEJM 1993*

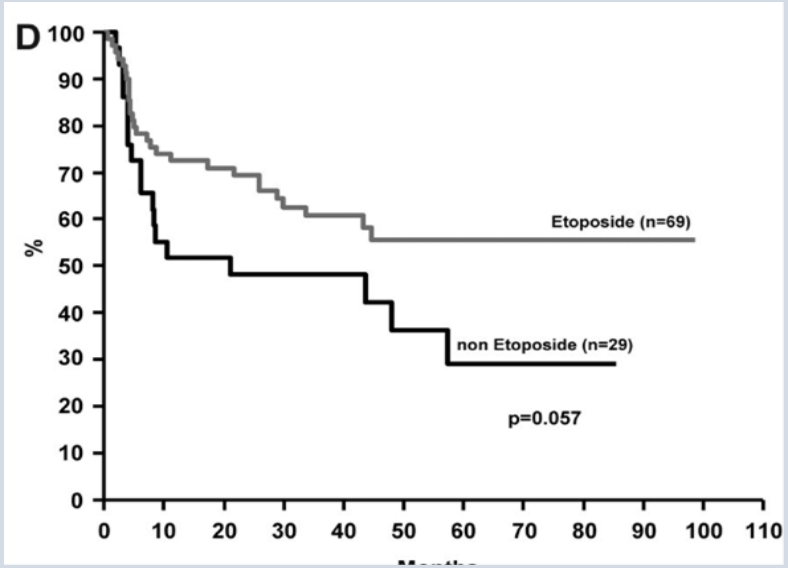
# Adding Etoposide to CHOP




**EFS, age 18-60 years**



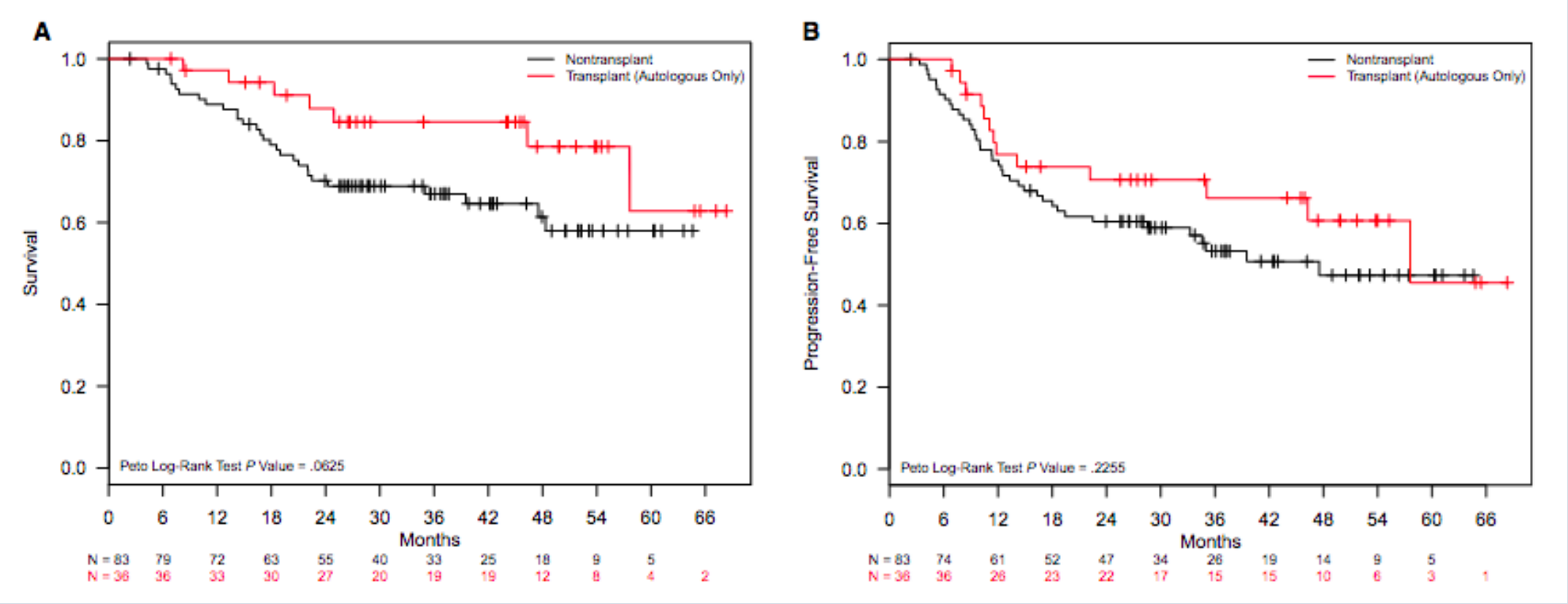

**ALK+ ALCL: EFS, age 18-60 years**




**Other major subtypes: EFS, age 18-60 years**

*Schmitz et al. Blood 2010*

# Consolidative autologous stem cell transplantation




*Park, et al. Cancer 2019*

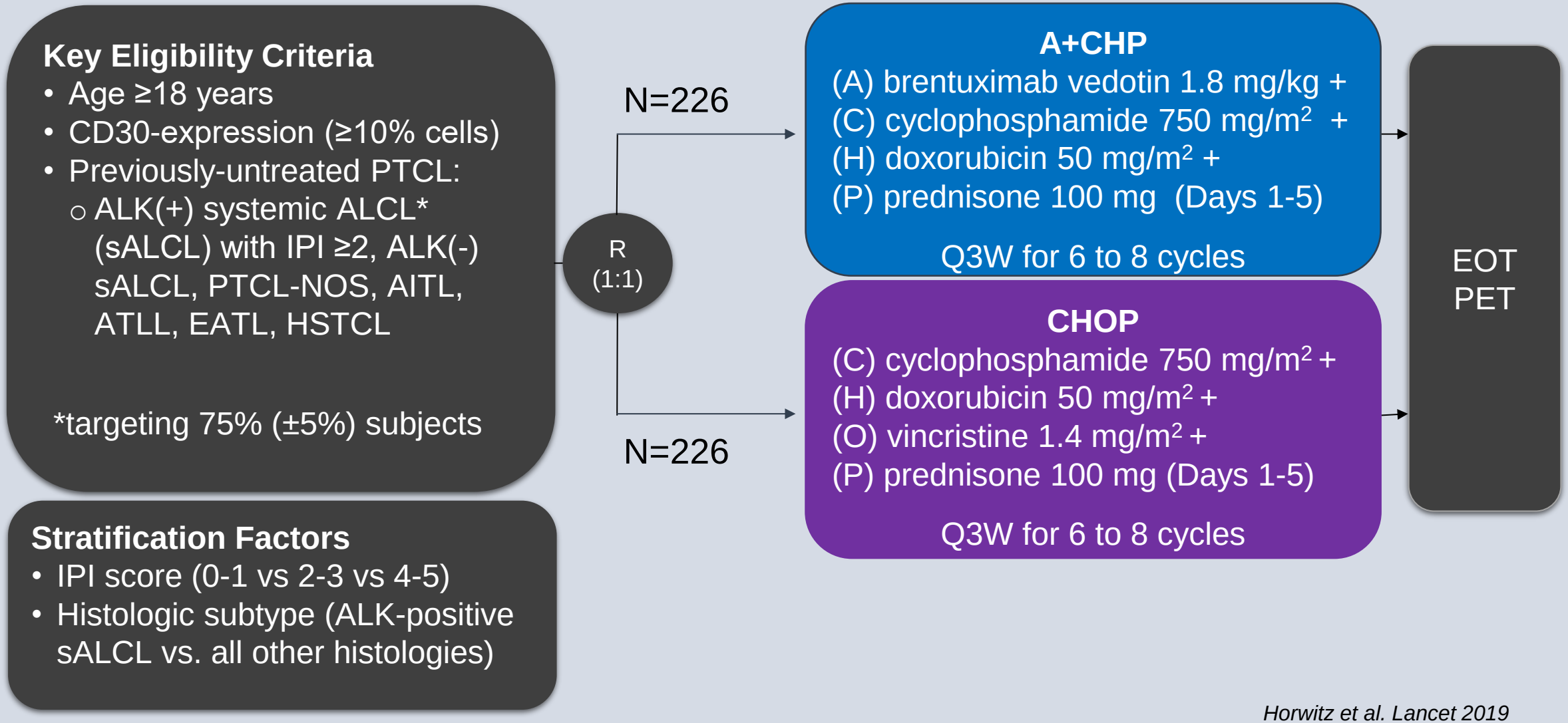
# The Phase 3 ECHELON-2 Trial: Results of a Randomized, Double-Blind, Active-Controlled Study of Brentuximab Vedotin and CHP (A+CHP) Versus CHOP in Previously Untreated Subjects with CD30-Expressing Peripheral T-Cell Lymphomas (PTCL)

Steven Horwitz, Owen A O'Connor, Barbara Pro, Tim Illidge, Michelle Fanale, Ranjana Advani, Nancy L Bartlett, Jacob Haaber Christensen, Franck Morschhauser, Eva Domingo-Domenech, Giuseppe Rossi, Won Seog Kim, Tatyana Feldman, Anne Lennard, David Belada, Árpád Illés, Kensei Tobinai, Kunihiro Tsukasaki, Su-Peng Yeh, Andrei Shustov, Andreas Hüttmann, Kerry J Savage, Sam Yuen, Swaminathan Iyer, Pier Luigi Zinzani, Zhaowei Hua, Meredith Little, Shangbang Rao, Joseph Woolery, Thomas Manley, Lorenz Trümper

American Society of Hematology Annual Meeting; San Diego, California, December 1-4, 2018, Abstract #997

*Lancet 2019*

# ECHELON-2 Study Design




*Horwitz et al. Lancet 2019*

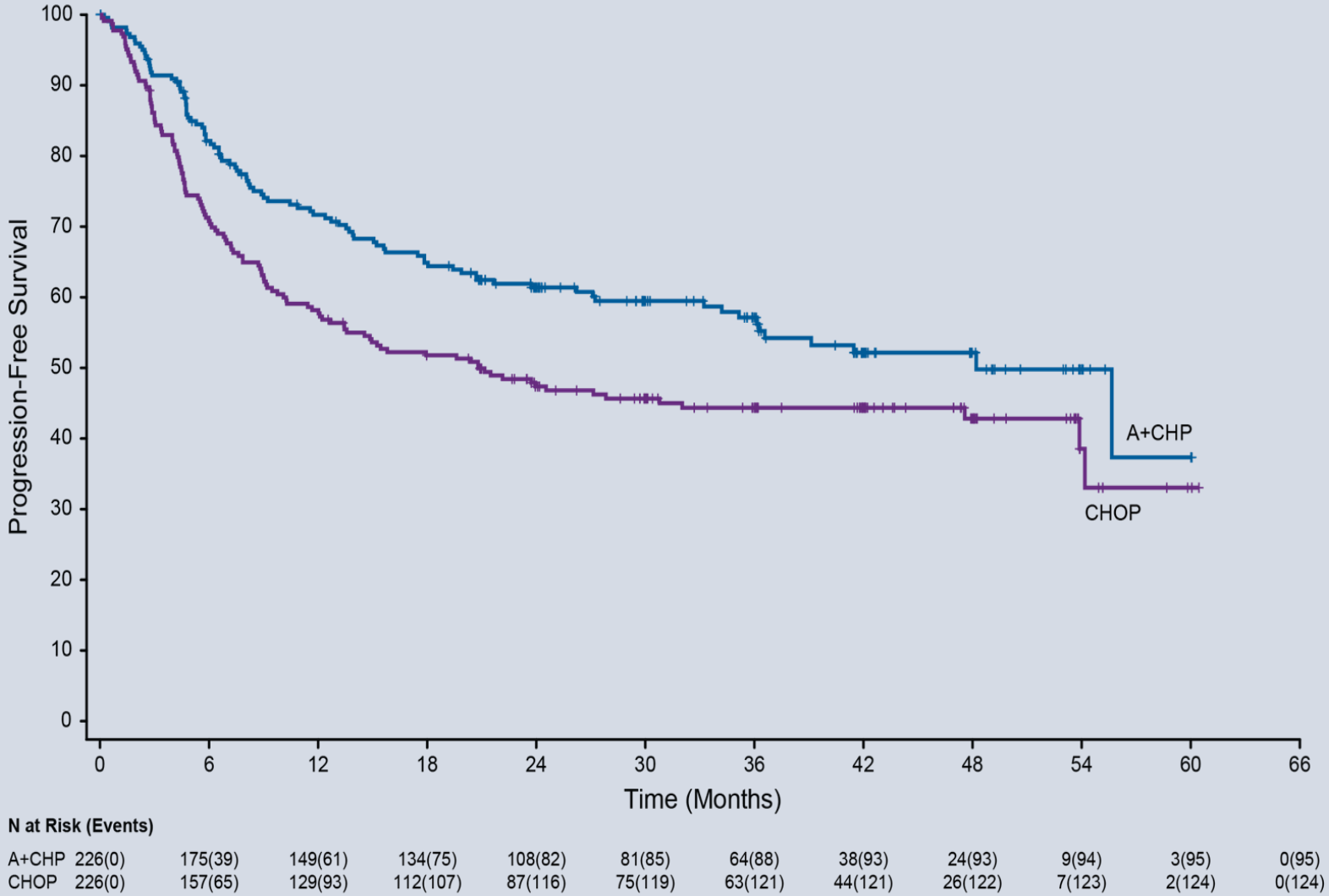
# ECHELON-2: Baseline Characteristics

| | A+CHP (N=226) | CHOP (N=226) |
|---|---|---|
| Male, n (%) | 133 (59) | 151 (67) |
| Age in years, median (range) | 58 (18-85) | 58 (18-83) |
| IPI score, n (%) | | |
| 0-1 | 52 (23) | 48 (21) |
| 2-3 | 141 (62) | 145 (64) |
| 4-5 | 33 (15) | 33 (15) |

| | A+CHP (N=226) | CHOP (N=226) |
|---|---|---|
| Stage III/IV disease, n (%) | 184 (81) | 180 (80) |
| Disease Diagnosis, n (%) | | |
| sALCL | 162 (72) | 154 (68) |
| ALK+ | 49 (22) | 49 (22) |
| ALK- | 113 (50) | 105 (46) |
| PTCL-NOS | 29 (13) | 43 (19) |
| AITL | 30 (13) | 24 (11) |
| ATLL | 4 (2) | 3 (1) |
| EATL | 1 (0) | 2 (1) |

*Horwitz et al. Lancet 2019*

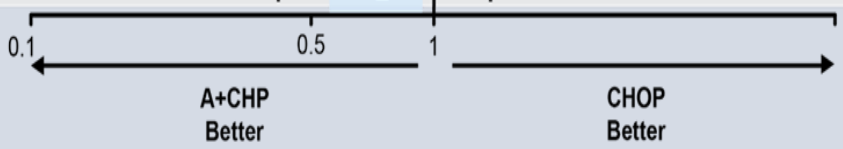
# ECHELON-2: PFS




*Horwitz et al. Lancet 2019*

# ECHELON-2: Prespecified Subset Analyses

| ITT Subgroups | Event/N A+CHP | Event/N CHOP | Hazard Ratio (95% CI) |
|---|---|---|---|
| Overall | 95/226 | 124/226 | 0.71 (0.54, 0.93) |
| IPI Score | | | |
| 0–1 | 18/52 | 27/48 | 0.53 (0.29, 0.97) |
| 2–3 | 56/141 | 77/145 | 0.71 (0.50, 1.00) |
| 4–5 | 21/33 | 20/33 | 1.03 (0.55, 1.92) |
| Age | | | |
| <65 years | 54/157 | 75/156 | 0.67 (0.47, 0.95) |
| ≥65 years | 41/69 | 49/70 | 0.70 (0.46, 1.08) |
| Gender | | | |
| Male | 59/133 | 80/151 | 0.80 (0.57, 1.13) |
| Female | 36/93 | 44/75 | 0.49 (0.31, 0.78) |
| Baseline ECOG Status | | | |
| 0/1 | 76/174 | 105/179 | 0.66 (0.49, 0.89) |
| 2 | 19/51 | 19/47 | 0.98 (0.51, 1.87) |
| Disease Stage | | | |
| I/II | 15/42 | 19/46 | 0.95 (0.48, 1.88) |
| III | 29/57 | 35/67 | 0.69 (0.42, 1.14) |
| IV | 51/127 | 70/113 | 0.64 (0.45, 0.93) |
| Disease Indication | | | |
| ALK-positive sALCL | 5/49 | 16/49 | 0.29 (0.11, 0.79) |
| ALK-negative sALCL | 50/113 | 60/105 | 0.65 (0.44, 0.95) |
| AITL | 18/30 | 13/24 | 1.40 (0.64, 3.07) |
| PTCL-NOS | 19/29 | 31/43 | 0.75 (0.41, 1.37) |

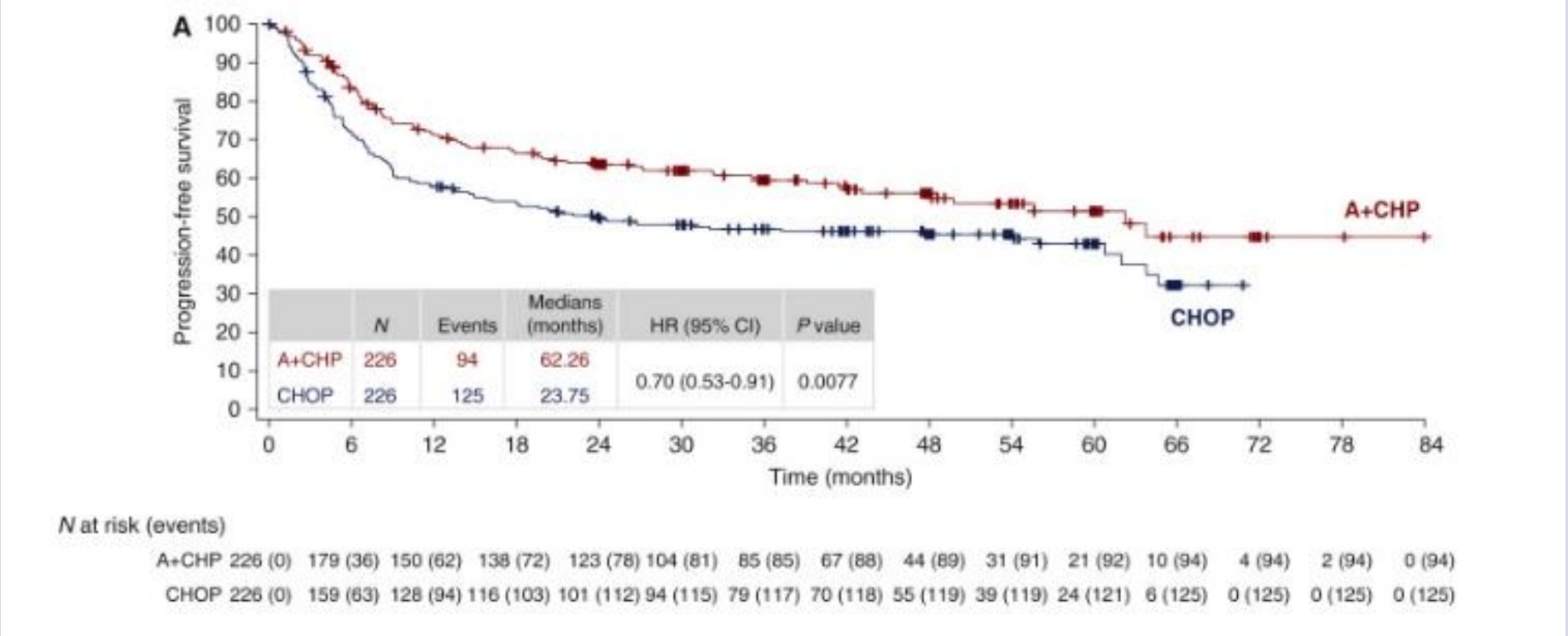



*Horwitz et al. Lancet 2019*

# PTCL Therapy: 2020-NCCN Guidelines Update

BV+CHP is recommended for front line therapy of CD30+ peripheral T-cell lymphomas

# ECHELON-2: 5-Year Follow-up

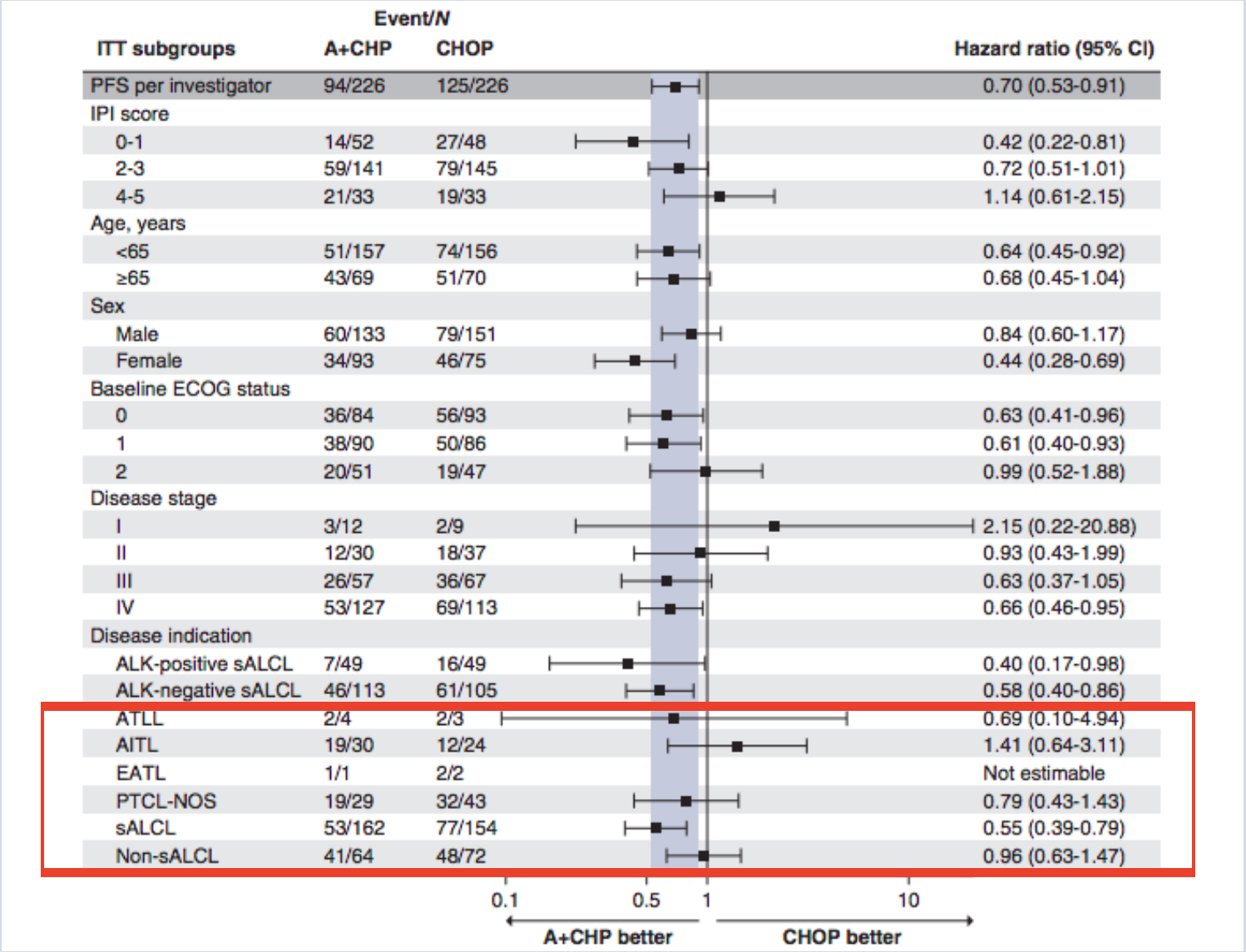



| | N | Events | Medians (months) | HR (95% CI) | P value |
|---|---|---|---|---|---|
| A+CHP | 226 | 94 | 62.26 | 0.70 (0.53-0.91) | 0.0077 |
| CHOP | 226 | 125 | 23.75 | | |

- 30% reduction in progression events with A+CHP vs CHOP
- 59% ORR with brentuximab retreatment after A+CHP

*Horwitz et al. Ann Oncol 2022*

# ECHELON-2: 5-Year Follow-up



| ITT subgroups | Event/*N* A+CHP | Event/*N* CHOP | Hazard ratio (95% CI) |
|---|---|---|---|
| PFS per investigator | 94/226 | 125/226 | 0.70 (0.53-0.91) |
| IPI score | | | |
| 0-1 | 14/52 | 27/48 | 0.42 (0.22-0.81) |
| 2-3 | 59/141 | 79/145 | 0.72 (0.51-1.01) |
| 4-5 | 21/33 | 19/33 | 1.14 (0.61-2.15) |
| Age, years | | | |
| <65 | 51/157 | 74/156 | 0.64 (0.45-0.92) |
| ≥65 | 43/69 | 51/70 | 0.68 (0.45-1.04) |
| Sex | | | |
| Male | 60/133 | 79/151 | 0.84 (0.60-1.17) |
| Female | 34/93 | 46/75 | 0.44 (0.28-0.69) |
| Baseline ECOG status | | | |
| 0 | 36/84 | 56/93 | 0.63 (0.41-0.96) |
| 1 | 38/90 | 50/86 | 0.61 (0.40-0.93) |
| 2 | 20/51 | 19/47 | 0.99 (0.52-1.88) |
| Disease stage | | | |
| I | 3/12 | 2/9 | 2.15 (0.22-20.88) |
| II | 12/30 | 18/37 | 0.93 (0.43-1.99) |
| III | 26/57 | 36/67 | 0.63 (0.37-1.05) |
| IV | 53/127 | 69/113 | 0.66 (0.46-0.95) |
| Disease indication | | | |
| ALK-positive sALCL | 7/49 | 16/49 | 0.40 (0.17-0.98) |
| ALK-negative sALCL | 46/113 | 61/105 | 0.58 (0.40-0.86) |
| ATLL | 2/4 | 2/3 | 0.69 (0.10-4.94) |
| AITL | 19/30 | 12/24 | 1.41 (0.64-3.11) |
| EATL | 1/1 | 2/2 | Not estimable |
| PTCL-NOS | 19/29 | 32/43 | 0.79 (0.43-1.43) |
| sALCL | 53/162 | 77/154 | 0.55 (0.39-0.79) |
| Non-sALCL | 41/64 | 48/72 | 0.96 (0.63-1.47) |

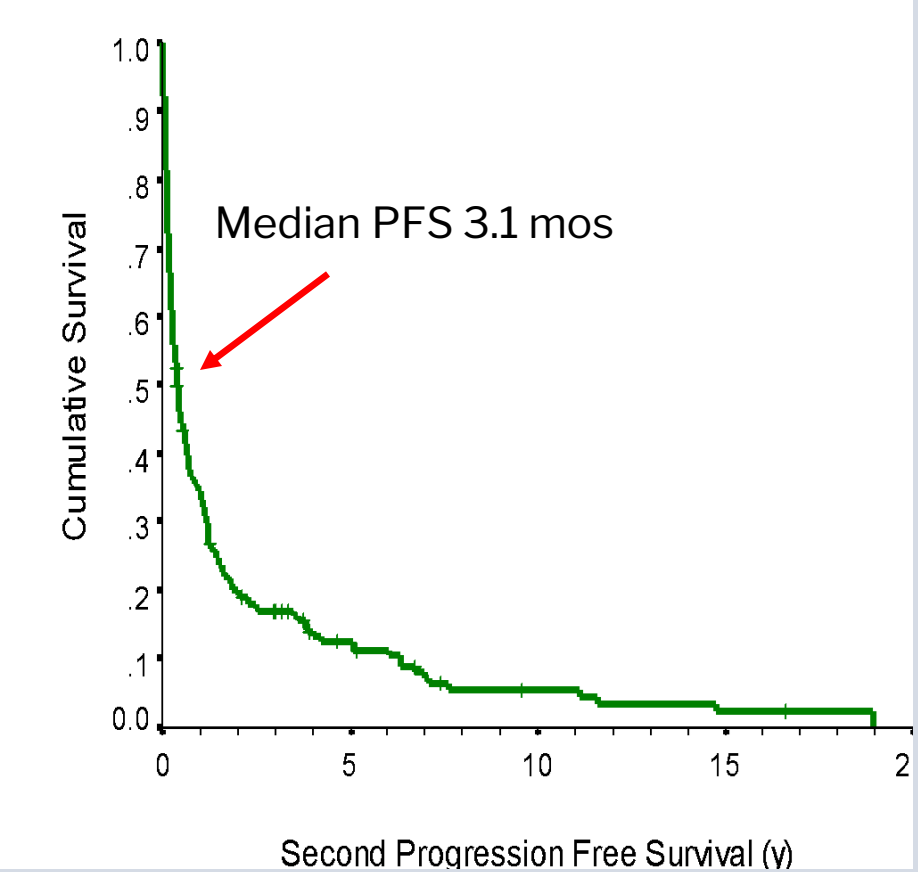


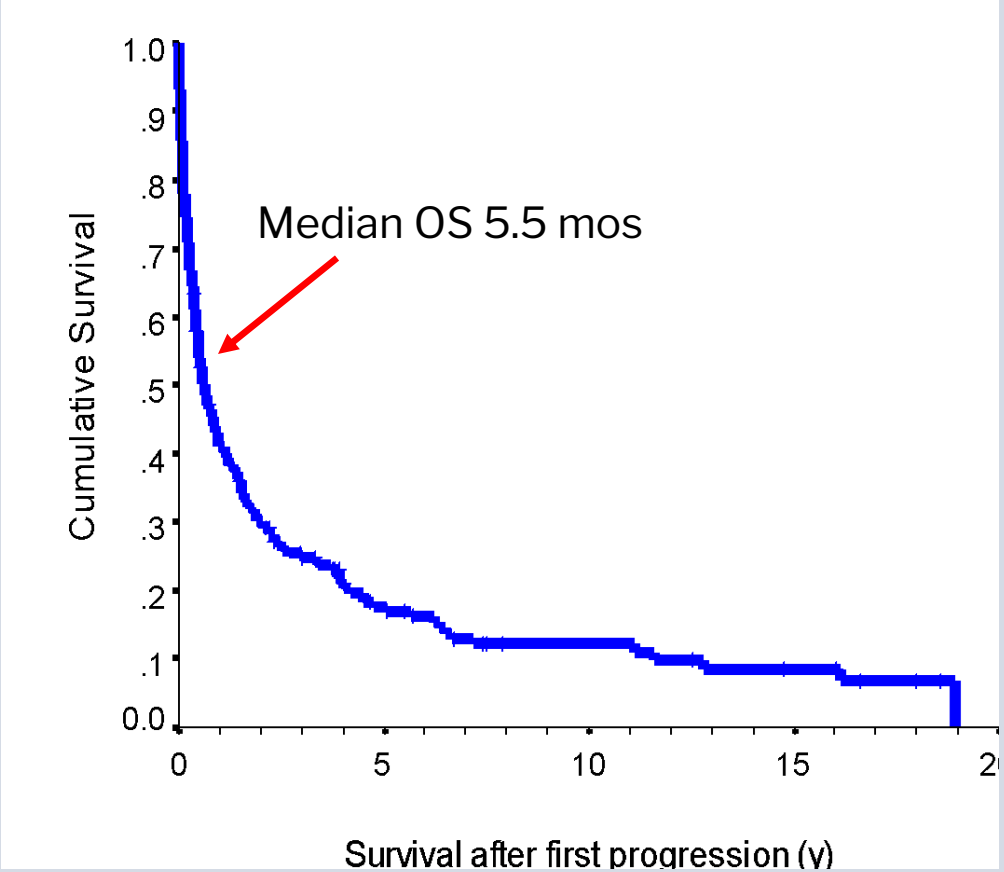
*Horwitz et al. Ann Oncol 2022*

# Summary

- PTCL is generally associated with poor outcomes with the exception of ALK+ ALCL  and ALK- ALCL with DUSP22-IRF4 rearrangements
- First-line therapy often results in inadequate outcomes for many PTCL patients
  - CD30+ : Brentuximab-CHP
  - CD30-: CHO(E)P
  - Clinical trials are preferred!
- Consolidative autologous stem cell transplant is considered in CR1 for ALK+ ALCL with high IPI and all other PTCL histologies

# Survival in PTCL Post 1st Relapse or Progression

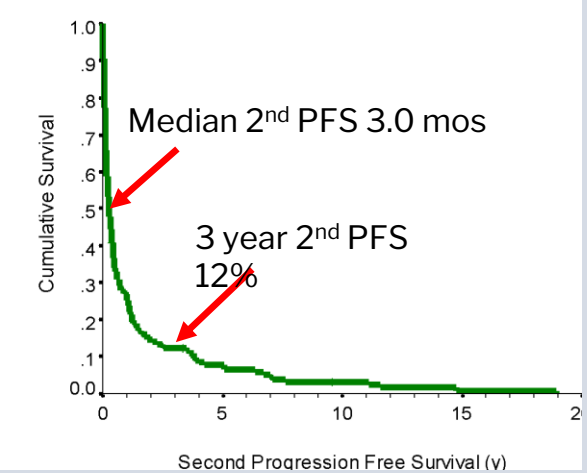


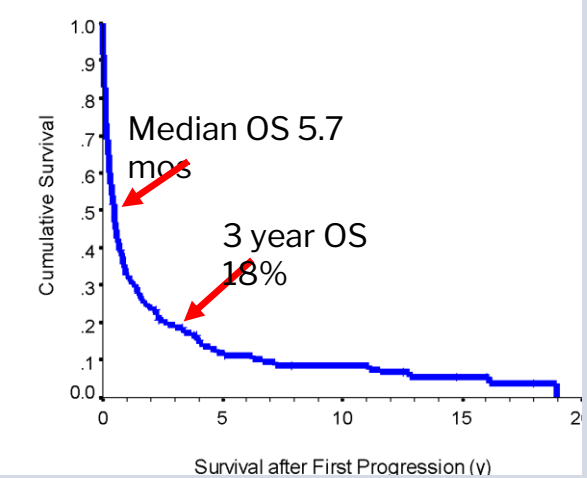



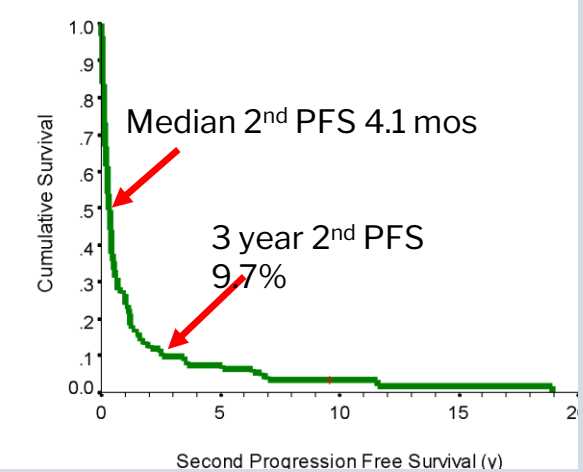

*Mak et al. JCO 2013*

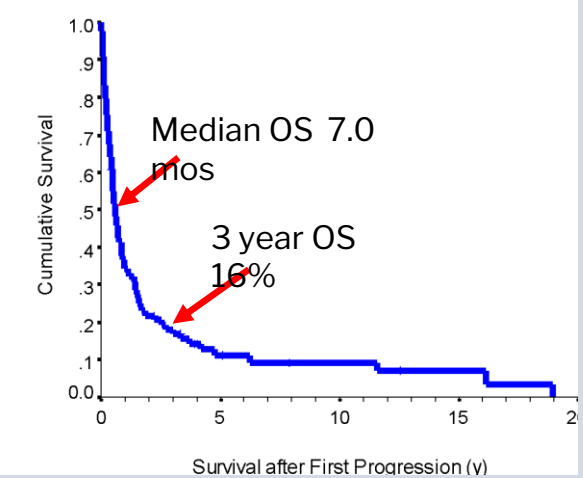
# Survival in PTCL Post 1st Relapse or Progression

**Patients not treated with chemotherapy**




**Patients treated with chemotherapy**

**Historical chemotherapy does not improve outcomes in relapsed or refractory PTCL**

*Mak et al. JCO 2013*

# Approved Agents in R/R PTCL

- Pralatrexate
- Belinostat
- Brentuximab Vedotin for CD30+ disease
- Romidepsin (BMS withdrew approval in 2021)
- Combination chemotherapy
  - ICE
  - GDP
  - DHAP
  - ESHAP

# **PROPEL:** Phase II Trial of Pralatrexate in R/R PTCL

- Population: 115 patients with PTCL who failed ≥1 prior systemic therapy
- Treatment regimen: Pralatrexate 30 mg/m$^2$, IV weekly for 6 weeks in 7-week cycles

| Response | Independent Review Committee Analysis (n = 109) |
|---|---|
| **Overall Response Rate** | 32 (29%) |
| Complete response | 12 (11%) |
| Partial response | 20 (18%) |
| Median DOR, mo (95% CI) | 10.1 (3.4-NE) |
| Median PFS, mo (95% CI) | 3.5 (1.7-4.8) |
| Median OS, mo (95% CI) | 14.5 (10.6-22.5) |

- Most common grade ¾ AE: thrombocytopenia (32%), neutropenia (22%), anemia (18%), mucositis (22%)

*O'Connor et al. JCO 2011*

# **BELIEF:** Phase II Trial of Belinostat in R/R PTCL

- Population: 129 patients with PTCL who failed ≥1 prior systemic therapy
- Treatment regimen: Belinostat 1000 mg/m$^2$, IV days 1-5 every 21 days

| Response | Efficacy Analysis (n = 120) |
|---|---|
| **Overall Response Rate** | 31 (26%) |
| Complete response | 13 (11%) |
| Partial response | 18 (15%) |
| Median DOR, mo (95% CI) | 13.6 (4.9-29.4) |
| Median PFS, mo (95% CI) | 1.6 (1.4-2.7) |
| Median OS, mo (95% CI) | 7.9 (6.1-13.9) |

- Most common grade ¾ AE: anemia (11%), thrombocytopenia (7%), dyspnea (6%) and neutropenia (6%)

*O'Connor et al. JCO 2015*

# **BELIEF**: Response by CPRG Lymphoma Subtype

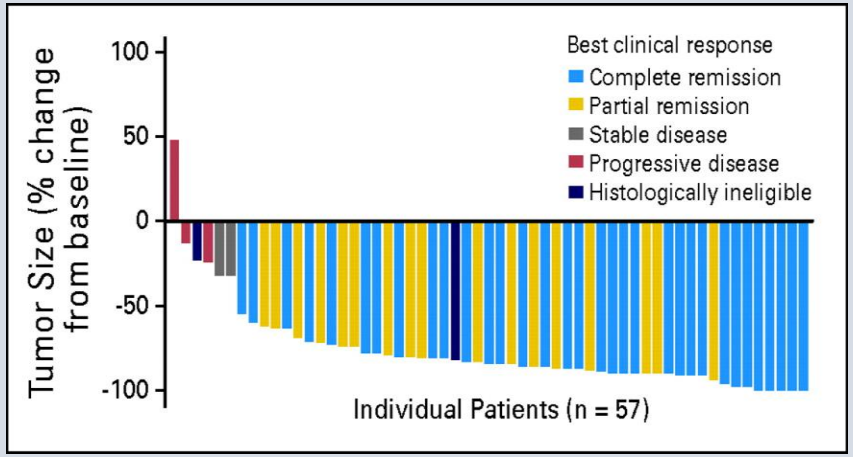
| CPRG Lymphoma Diagnosis | Subset n (%) | Responders n (%) |
|---|---|---|
| PTCL, NOS | 77 (64) | 18 (23) |
| AITL | 22 (18) | 10 (46) |
| ALCL, ALK-negative | 13 (11) | 2 (15) |
| ALCL, ALK-positive | 2 (2) | 0 (0) |
| Enteropathy-associated TCL | 2 (2) | 0 (0) |
| Extranodal NK/TCL, nasal type | 2 (2) | 1 (50) |
| Hepatosplenic TCL | 2 (2) | 0 (0) |

*O'Connor et al. JCO 2015*

# Phase II Trial of Brentuximab in R/R ALCL

- Population: 58 patients with systemic ALCL who failed ≥1 prior systemic therapy
- Treatment regimen: Brentuximab 1.8 mg/m$^2$, IV every 3 weeks

| Response | Efficacy Analysis (n = 58) |
|---|---|
| **Overall Response Rate** | 50 (86%) |
| Complete response | 33 (57%) |
| Partial response | 17 (29%) |
| Median DOR, mo (95% CI) | 12.6 (5.7-NE) |
| Median PFS, mo (95% CI) | 13.3 (6.9-NE) |




- Most common grade ¾ AE: neutropenia (21%), thrombocytopenia (14%) and peripheral sensory neuropathy (12%)

*Pro et al. JCO 2012*

# Off-label Agents in R/R PTCL

- Romidepsin (BMS withdrew approval in 2021)
- Duvelisib
- Azacitidine
- EZH2 inhibitors: Valematostat
- JAK inhibitors: Golidocitinib, ruxolitinib
- Clinical trials preferred!

# Phase II Trial of Romidepsin in R/R PTCL

- Population: 131 patients with PTCL who failed ≥1 prior systemic therapy
- Treatment regimen: Romidepsin 14 mg/m$^2$, IV days 1, 8, and 15 q 28 days × 6 cycles; continued beyond 6 cycles in responding patients

| Response | Independent Review Committee Analysis (n = 130) |
|---|---|
| **Overall Response Rate** | 33 (25%) |
| Complete response | 19 (15%) |
| Median DOR, mo | 17 |

- Responses reported in PTCL (not otherwise specified) (29%), angioimmunoblastic TCL (33%), and ALK- ALCL (24%)
- Most common grade ¾ AE: thrombocytopenia (24%), neutropenia (20%), infections (19%)
- Withdrawn by BMS for PTCL in 2021 due to a negative phase III trial of Romidepsin-CHOP vs CHOP in untreated PTCL
  - Romidepsin-CHOP associated with higher rates of anemia

*Coiffier et al. JCO 2012*

# **PRIMO:** Phase II Trial of Duvelisib in R/R PTCL

- Population: 101 patients with PTCL who failed ≥1 prior systemic therapy and with CD4 lymphocyte count of ≥50/mm$^3$
- Treatment regimen: Duvelisib 75 mg PO BID for 2 cycles followed by 25 mg BID

| Response | Independent Review Committee Analysis (n = 101) |
|---|---|
| **Overall Response Rate** | 49 (49%) |
| Complete response | 34 (34%) |
| Partial response | 15 (15%) |
| Median PFS, mo (95% CI) | 3.6 (3.2-8.1) |
| Median DOR, mo (95% CI) | 7.7 (5.5-9.4) |

- Median PFS stratified by baseline histology was 3.5 months for PTCL-NOS, 9.1 months for AITL and 1.5 months for ALCL
- Treatment related AEs associated with death: pneumonitis (1), EBV associated lymphoproliferative disorder (1), sepsis (1)

*Zinzani et al. Hemasphere 2022*

# **ORACLE:** Phase III Trial of Oral Azacytidine in R/R AITL

- Population: 86 patients with R/R AITL or nodal follicular helper T-cell lymphoma
- Treatment regimen: randomized between CC-486 300 mg daily (200 mg in Asians) x14 out of 28 days and investigator's choice (gemcitabine, bendamustine, romidepsin)

| Response | CC-486 | Control | HR |
|---|---|---|---|
| Overall Response Rate (at 3 mo) | 33% | 43.2% | |
| Complete response (at 3 mo) | 11.9% | 22.7% | |
| **Median PFS, mo (95% CI)** | **5.6 (2.7-8.1)** | **2.8 (1.9-4.8)** | **0.634 (0.38-1.07)** |
| Median OS, mo (95% CI) | 18.4 (12.9-31.5) | 10.3 (4.2-13.5) | 0.557 (0.32-0.96) |

- Common AE (CC-486 vs control): neutropenia (43% vs 58%), thrombocytopenia (24% vs 49%), infections (36 vs 67%), GI disorders (71% vs 56%)
- Trial did not meet its primary endpoint (PFS), most likely due to an optimistic hypothesis of PFS improvement, resulting in a study which could be underpowered to detect a clinically meaningful difference

*Dupuis et al. Blood Supp 2022*

# **VALENTINE-PTCL01:** Valemetostat in R/R PTCL

- Population: 133 patients with R/R PTCL
- Treatment regimen: Oral Valemetostat 200 mg daily until disease progression or intolerable toxicity

| Response | Efficacy Analysis (n = 119) |
|---|---|
| **Overall Response Rate** | 52 (43.7%) |
| Complete response | 17 (14.3%) |
| Partial response | 35 (29.4%) |
| Median DOR, mo (95% CI) | 11.9 (7.8-NE) |

- 77 (57.9%) patients had grade 3-4 drug-related TEAE
- Common AE: thrombocytopenia (49.6%), anemia (35.3%), diarrhea (29.3%), dysgeusia (28.6%)

*Horwitz et al. Blood Supp 2023*

# **JACKPOT8:** Golidocitinib in R/R PTCL

- Population: 104 patients with R/R PTCL
- Treatment regimen: Oral Golidocitinib 150 mg daily until disease progression or intolerable toxicity

| Response | Efficacy Analysis (n = 88) |
|---|---|
| **Overall Response Rate** | 39 (44.3%) |
| Complete response | 21 (24%) |
| Partial response | 18 (20%) |
| Median PFS, mo | 5.6 |
| Median OS, mo | 19.4 |

- 61 (59%) patients had grade 3-4 drug-related TEAE
- Common AE: neutropenia (29%), lymphopenia (21%), thrombocytopenia (20%)
- Deaths due to TEAE occurred in 3 (3%) patients: 2 due to pneumonia and 1 due to confusional state

*Song et al. Lancet Oncol2024*

# Ruxolitinib in R/R PTCL

- Population: 52 patients with R/R PTCL Treatment regimen: Oral Ruxolitinib 20 mg twice daily until disease progression or intolerable toxicity

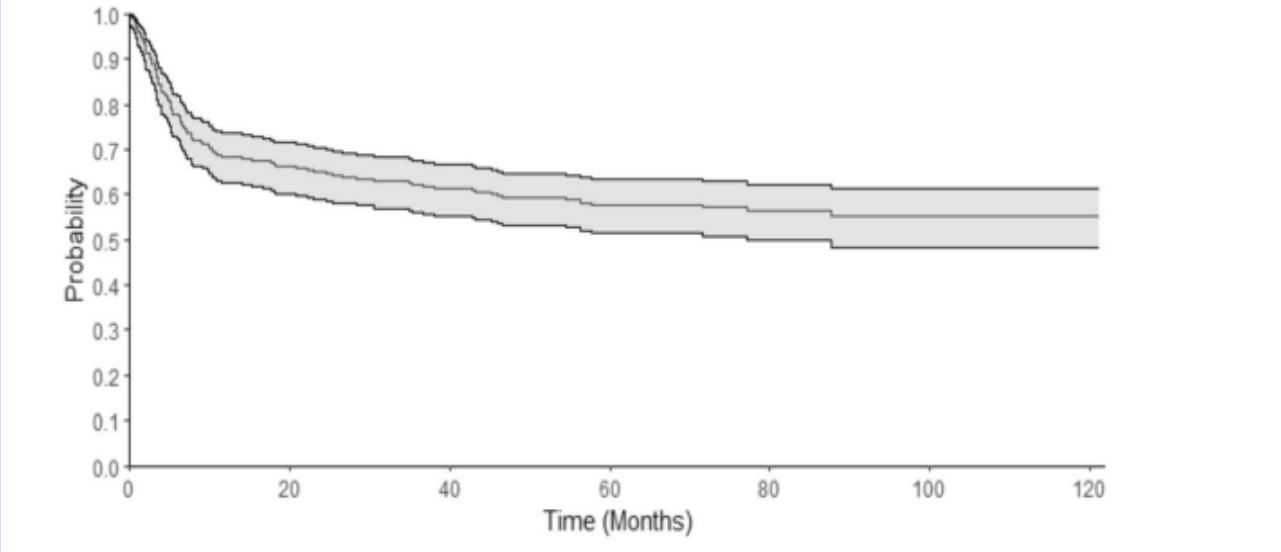
| Response | Efficacy Analysis (n = 52) |
|---|---|
| **Clinical Benefit Rate** | 18 (35%) |
| **Overall Response Rate** | 13 (25%) |
| Median PFS, mo (95% CI) | 2.8 (1.8-4.5) |
| Median OS, mo (95% CI) | 26.2 (11.5-NR) |

- Common AE: anemia (28%), neutropenia (19%), thrombocytopenia (17%)
- No discontinuations due to toxicity

*Moskowitz et al. Blood 2021*

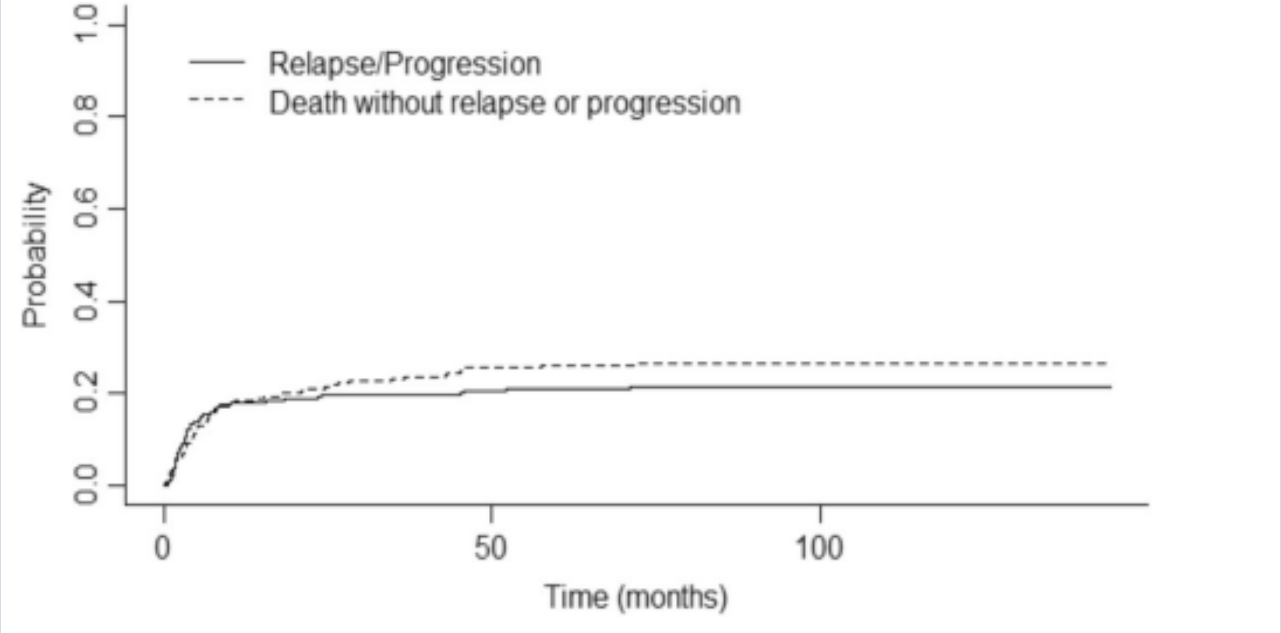
# Allogeneic Stem Cell Transplantation

Overall survival:
- 1year: 68%
- 2 year: 65%
- 4 years: 59%



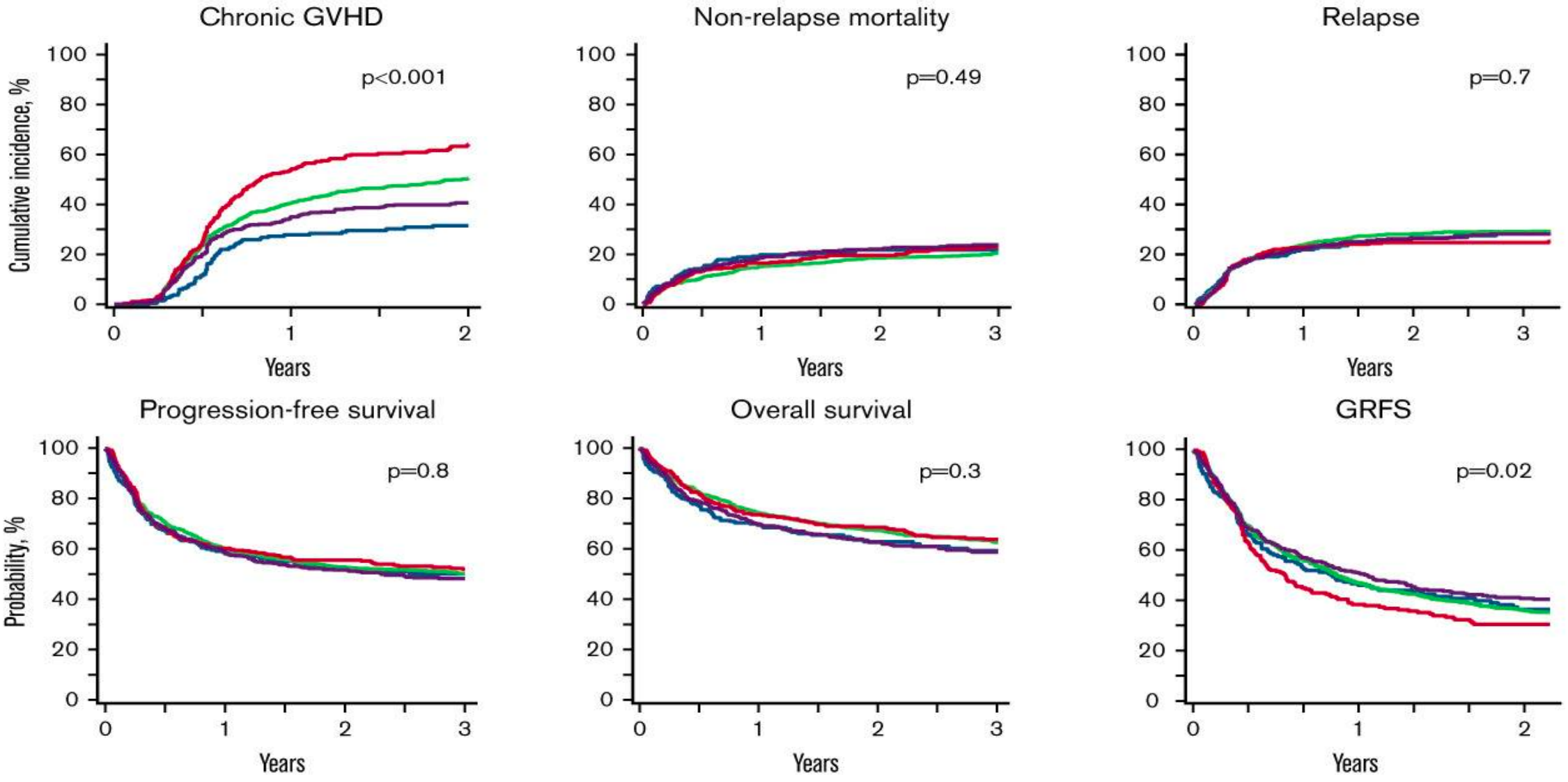

Incidence of relapse:
- 1 year: 18%
- 2 year: 19%

Treatment-related mortality:
- 1 year: 21%
- 2 year: 24%




*Mamez 2020*

Allogeneic transplantation for mature T-cell lymphomas
CIBMTR & EBMT analysis
N = 1942; Era 2008–18
Outcomes stratified by donor source

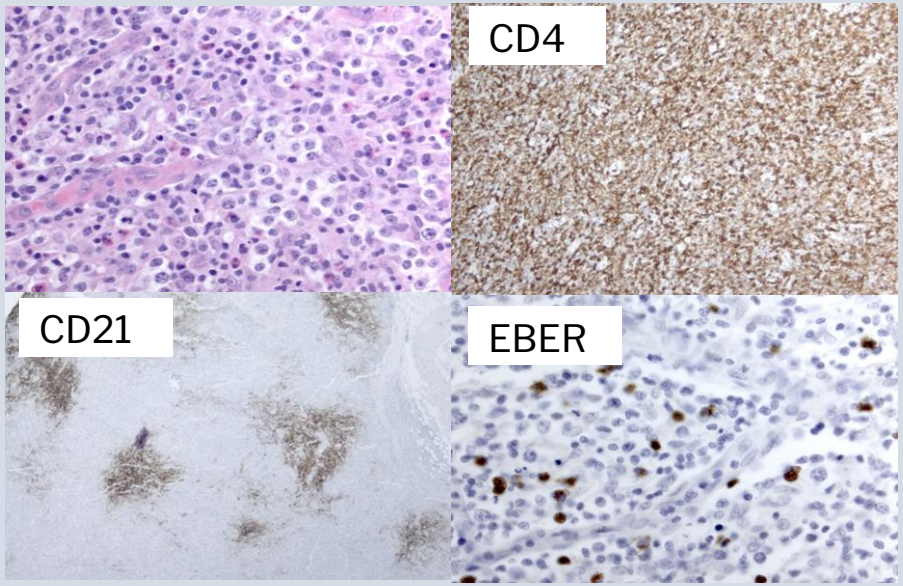


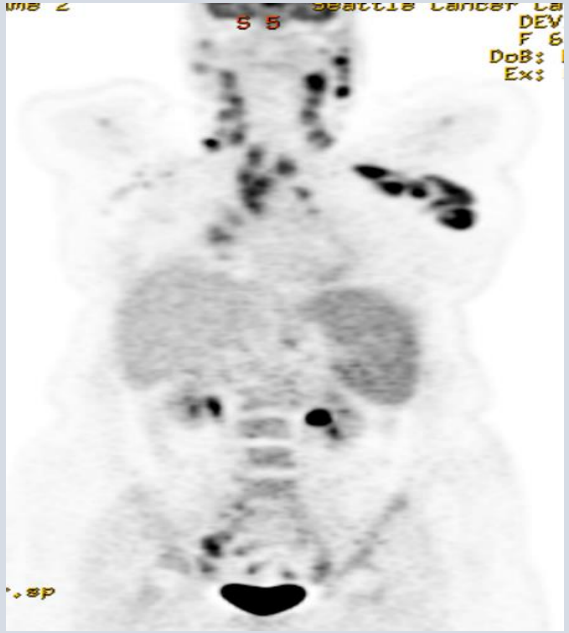

*Hamadani 2022*

# Summary

- Relapsed/Refractory PTCL is associated with poor outcomes
  - median OS <6 month
- Therapies approved in R/R PTCL
  - Pralatrexate (folate analogue)
  - Belinostat (histone deacetylase inhibitor)
  - Brentuximab for CD30+ disease (CD30 antibody drug conjugate)
  - Multi-agent chemotherapy
- Multiple therapies used off-label in R/R PTCL
- Allogeneic stem cell transplant is potentially curative with ORR 50% and should be considered for those who obtain a CR2

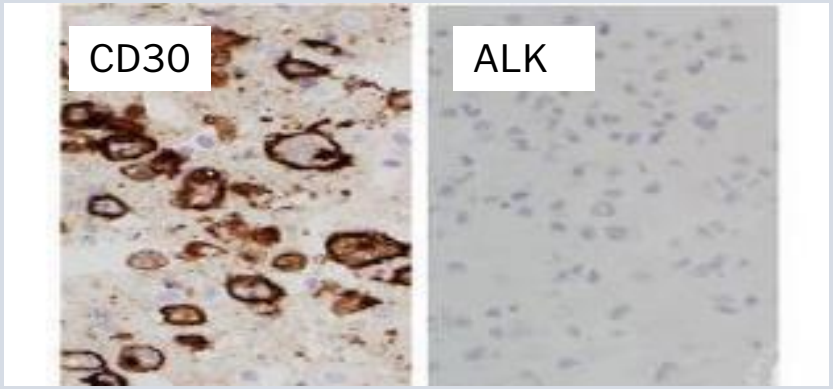
# Unique Subtypes of PTCL
## *Angioimmunoblastic T-cell Lymphoma*

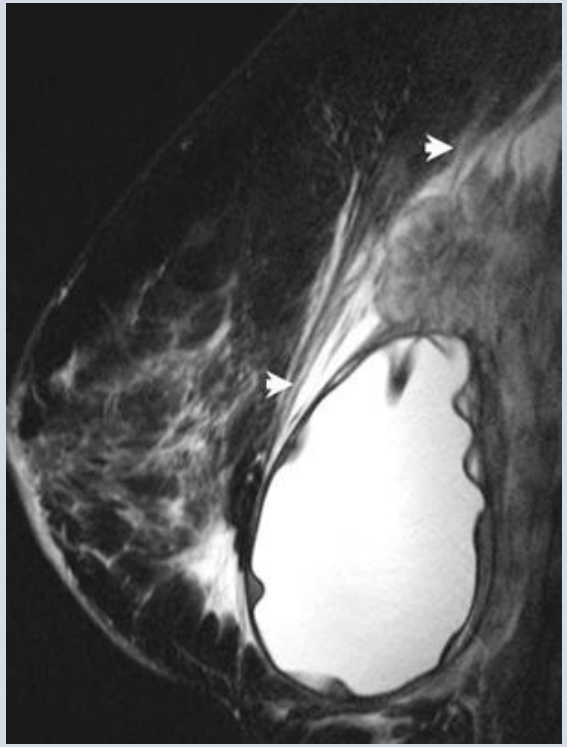


- Malignancy of CD4+ helper T-cells
- **Autoimmune phenomena** are a prominent feature, incl. polyarthritis, pruritic rash, ascites/effusions, thyroid disease, vasculitis, elevated ESR, eosinophilia, +Coombs
- Epigenetic deregulation is a prominent feature of pathogenesis; evaluate for **TET2, IDH1/2, RHOA, DNMT3A**
- May occasionally present with concurrent DLBCL or EBV; repeat biopsy of any persistent or new PET-positive lesions prior to additional therapy
- Treatment approach like PTCL-NOS
- Epigenetic or protein modifiers such as azacitidine, duvelisib, belinostat have proven to be effective

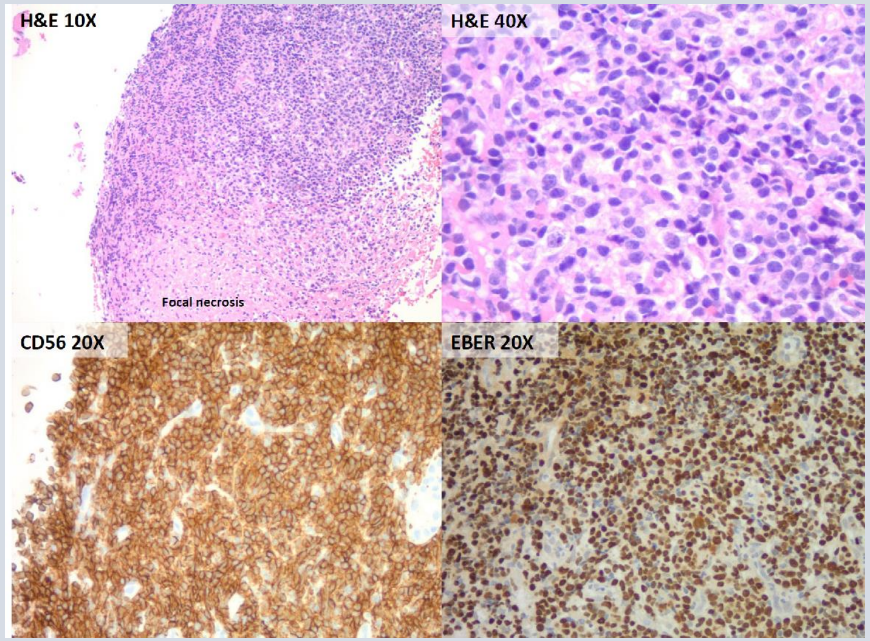
# Unique Subtypes of PTCL
## *Breast Implant-Associated ALK- Anaplastic Large Cell Lymphoma*

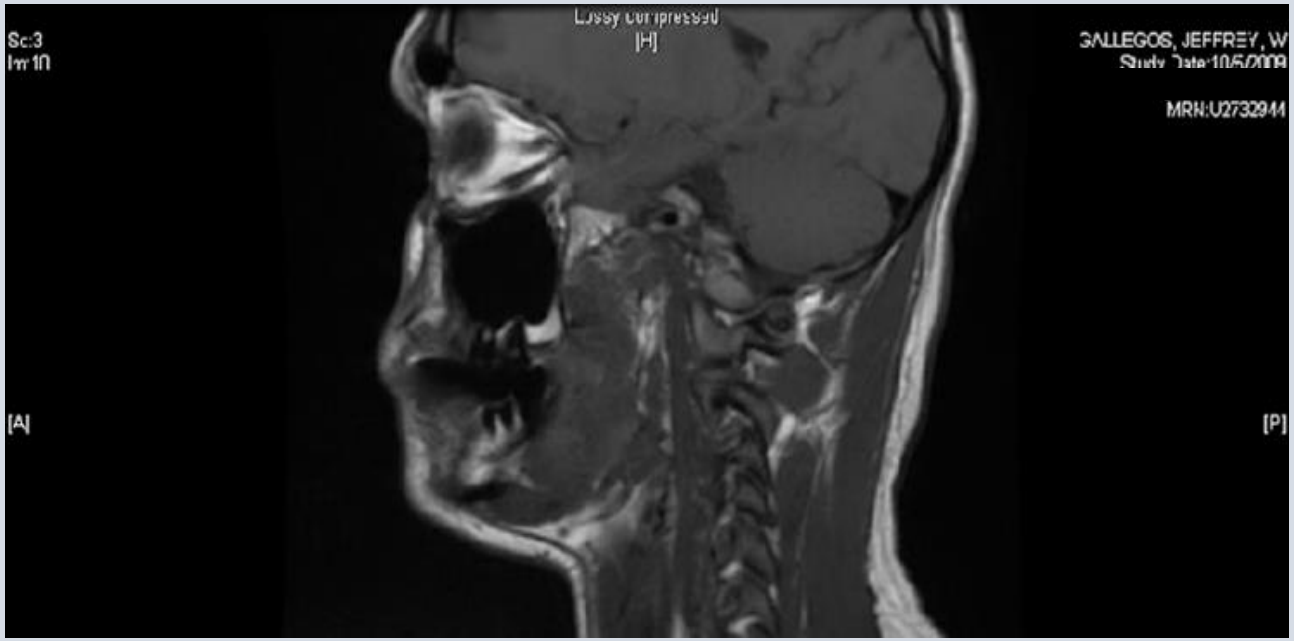


- **PTCL arising around a texture surfaced breast implant or surface device**, without invasion of underlying breast tissue
- Usually presents with periprosthetic effusion and breast asymmetry occurring greater than 1 year after implantation
- May requires sufficient volume of fluid (minimum 50 mL) or multiple systemic scar capsule biopsies to achieve diagnosis
- Tx: **total capsulectomy ± LN bx, removal of contralateral implant (followed by systemic therapy if advanced stage)**

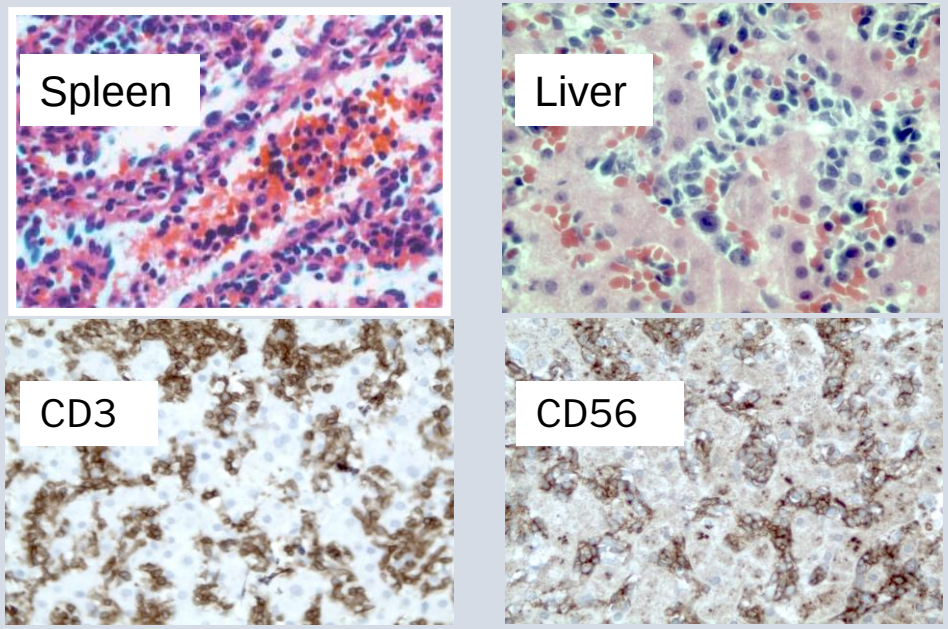
# Unique Subtypes of T-cell Lymphoma
## *Extranodal NK/T-cell Lymphoma, Nasal Type*

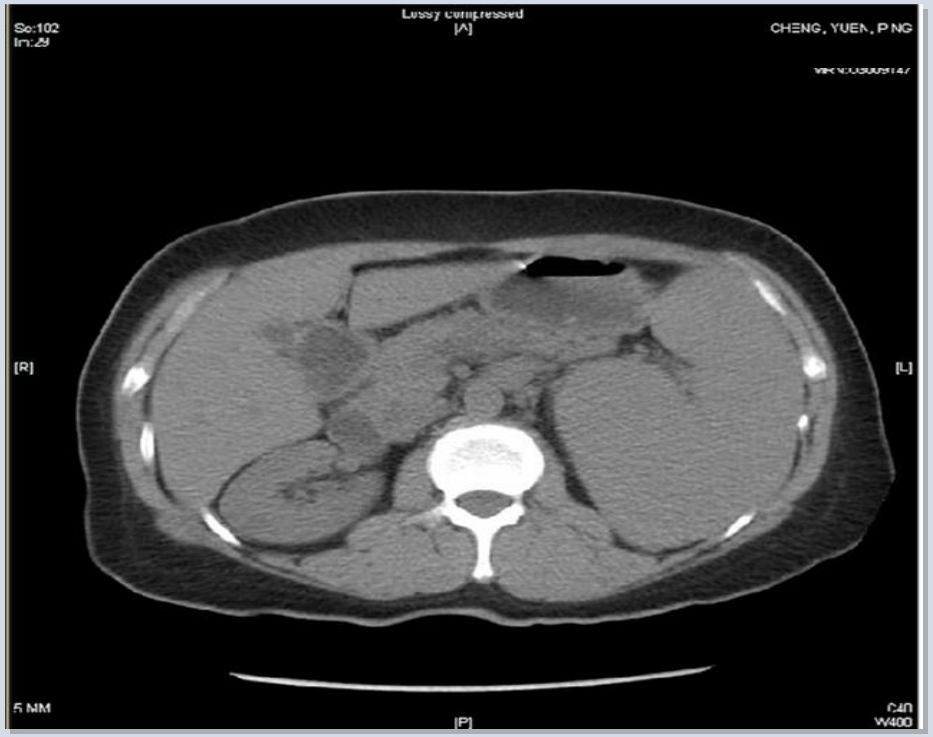



- High prevalence in Asian and Native American populations; HLA-DPB1 polymorphism
- Majority are **EBV positive**. Lack of normalization of EBV viremia should be considered indirect evidence of persistent disease
- Early stage – **combined modality tx** with  DeVIC, P-GEMOX; radiation for frail patients
- Advanced stage – **asparaginase-based chemotherapy**: SMILE, P-GEMOX +/- consolidative SCT in CR1
- Relapsed/refractory - **pembrolizumab**, nivolumab, brentuximab for CD30+ disease

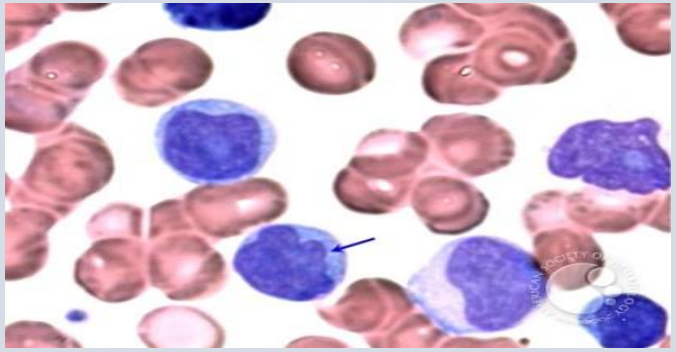
# Unique Subtypes of T-cell Lymphoma
## *Hepatosplenic T-cell Lymphoma*

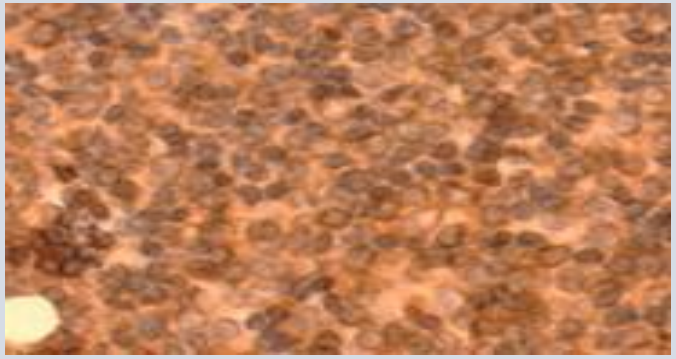


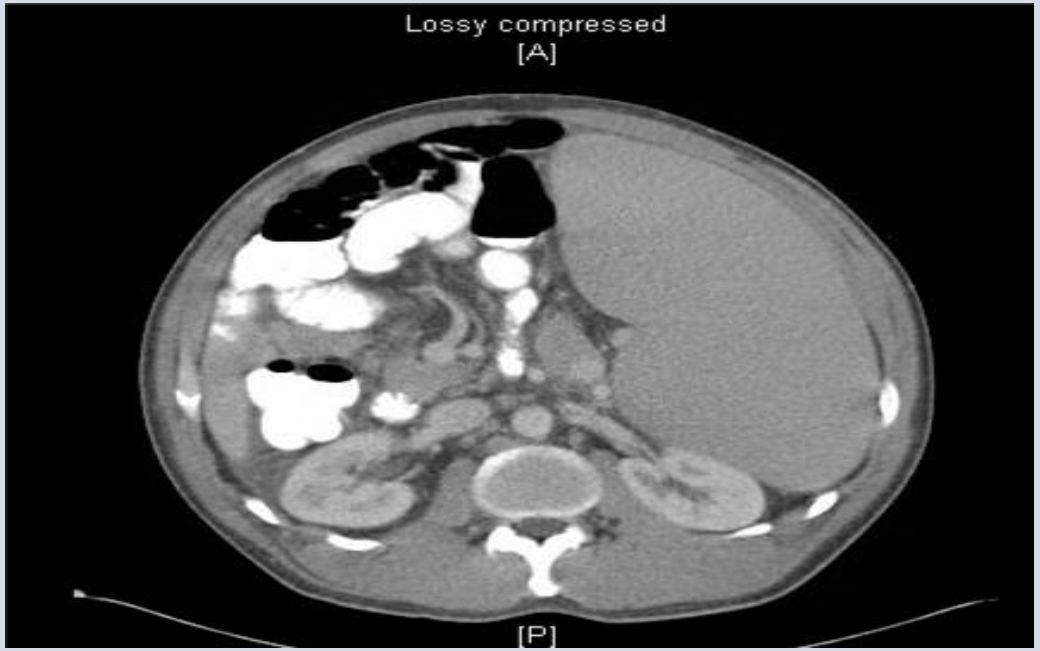




- Unique spleen, liver, bone marrow involvement in young males
- Considered the most aggressive PTCL subtype
- **Isochrome 7q and trisomy 8** are characteristic genetic features
- Repetitive bone marrow and liver biopsies are essential for dx and response assessment
- First-line therapy with ifosfamide-containing protocols **(ICE) followed by allogeneic SCT**

# Unique Subtypes of T-cell Lymphoma
## *T-cell Prolymphocytic Leukemia*



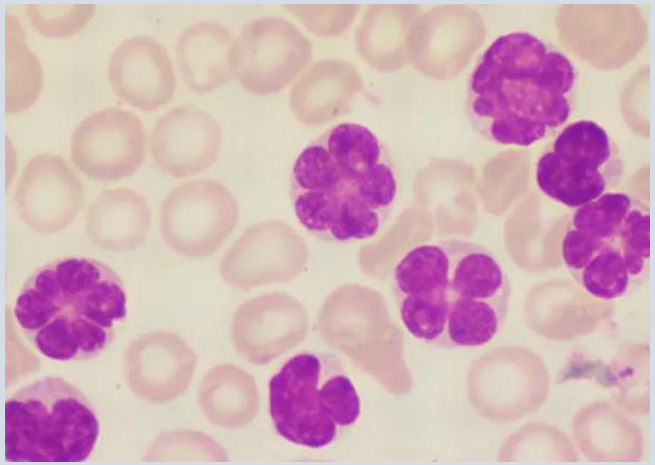





- More clinically aggressive than B-cell CLL; some patients might have initial indolent phase (3-12 months)
- **TRA and TCL1** translocations on **chromosome 14** are hallmark: inv(14)(q11q32) and t(14;14)(q11;q32)
- Innate chemotherapy resistance to typical B-CLL regimens; **alemtuzumab** (± pentostatin) is the most effective first-line treatment
- Consolidative allogeneic HCT considered in CR1

# Special Management Scenarios

- Adult T-cell Leukemia/Lymphoma
  - common in Caribbean islands and southern Japan
  - associated with human T-cell leukemia virus type 1 **(HTLV-1) infection**
  - Diagnosis requires peripheral blood or tissue histopathology (**distinct cloverleaf appearance**) and **+HTLV-1 serology**
  - Dose-adjusted EPOCH or brentuximab+CHP for CD30+ cases for acute/lymphoma subtypes
  - Observation or Zidovudine and interferon can be used for smoldering/chronic subtypes
  - **Mogamulizumab** found to be effective (approved in Japan)



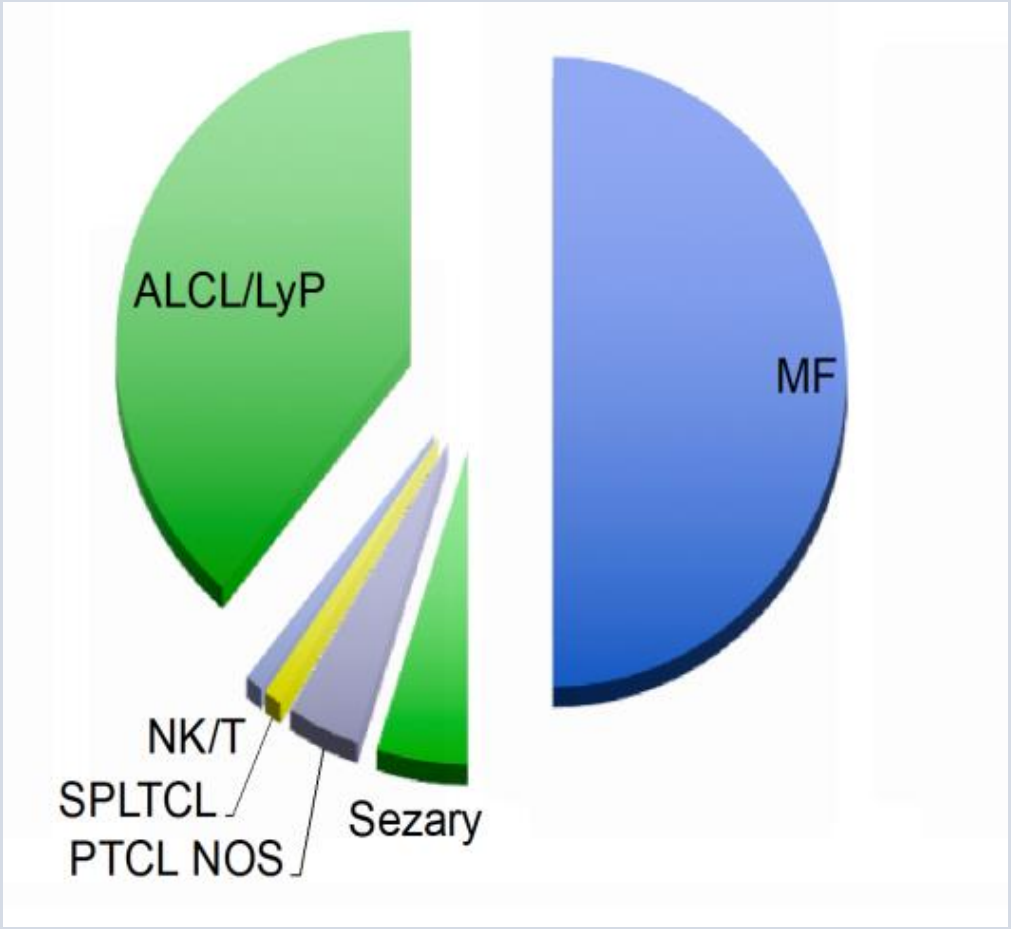
*Flower cells of leukemia. Blood 2010*

# Special Management Scenarios

- Large Granular Lymphocyte Disorder with Autoimmune Cytopenias
  - commonly associated with **autoimmune conditions** (rheumatoid arthritis)
  - most have indolent clinical course and can be observed
  - **STAT3 or STAT5B** mutations can be seen; STAT5B associated with aggressive course
  - **Immunomodulatory agents**: Low-dose oral Methotrexate, Cyclosporine A, Cyclophosphamide, Prednisone, Growth Factors
  - Alemtuzumab in low doses for R/R disease

# Cutaneous T-cell Lymphomas

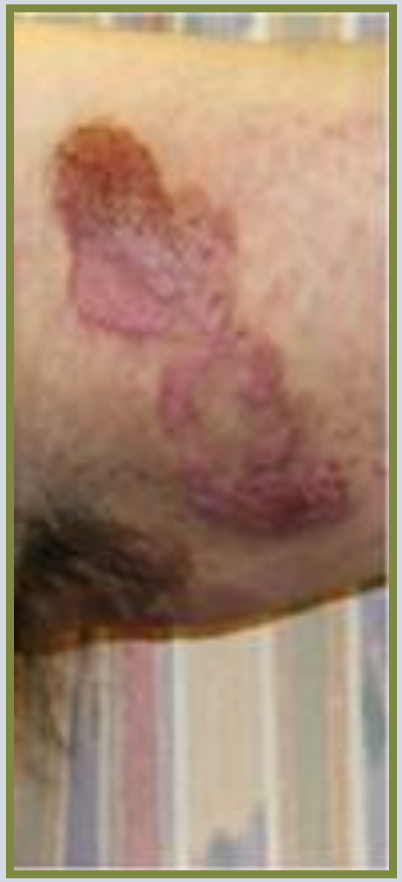
# Cutaneous T-Cell Lymphoma: Epidemiology



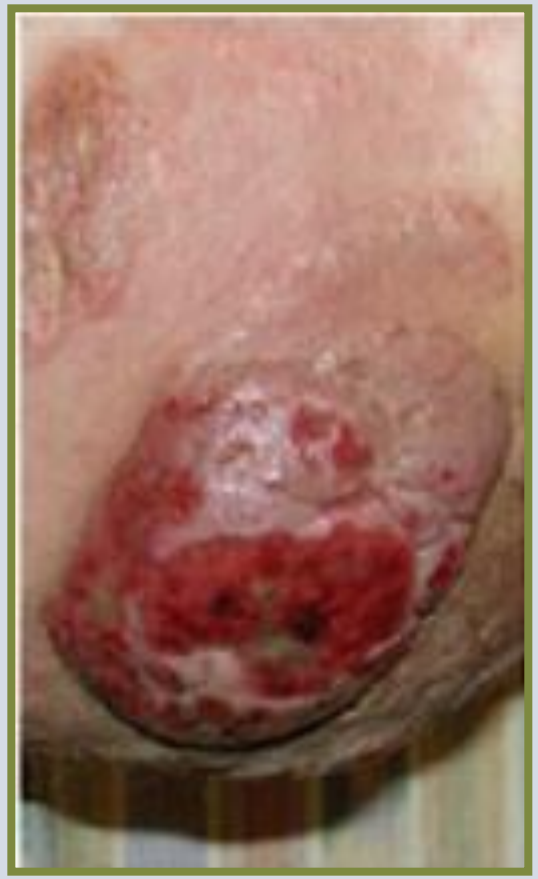

**Incidence:**
- 0.4/100,000
- 1,000 new cases/year

# Cutaneous T-Cell Lymphoma: Cutaneous Manifestations

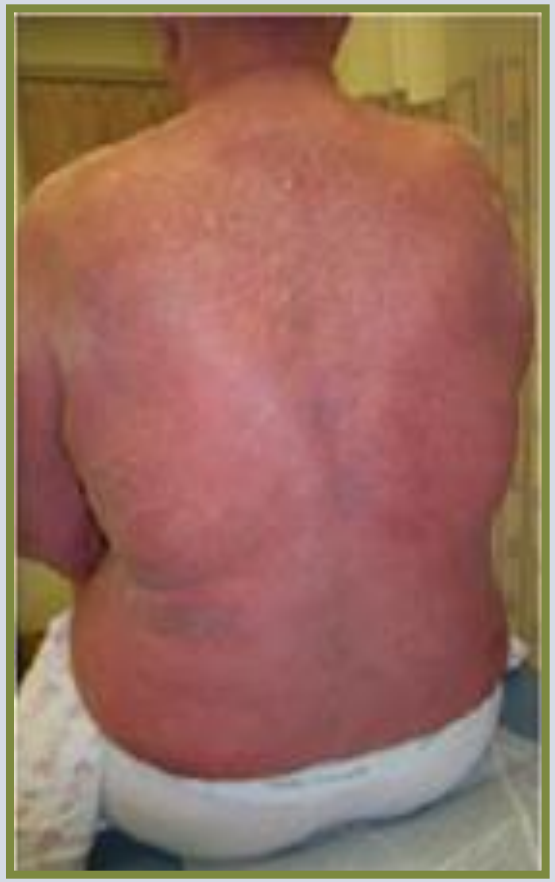
Patch



Plaque



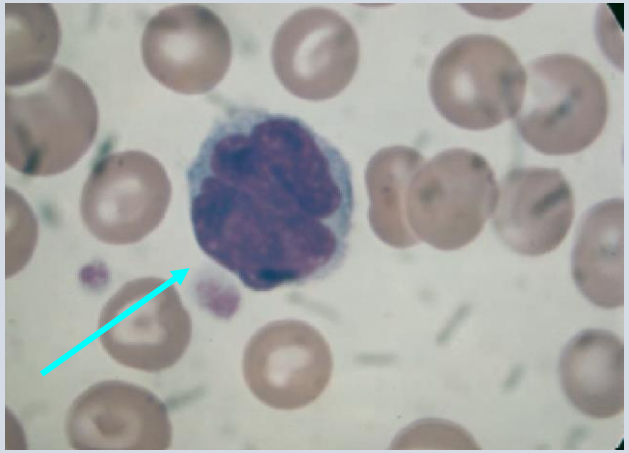
Tumor



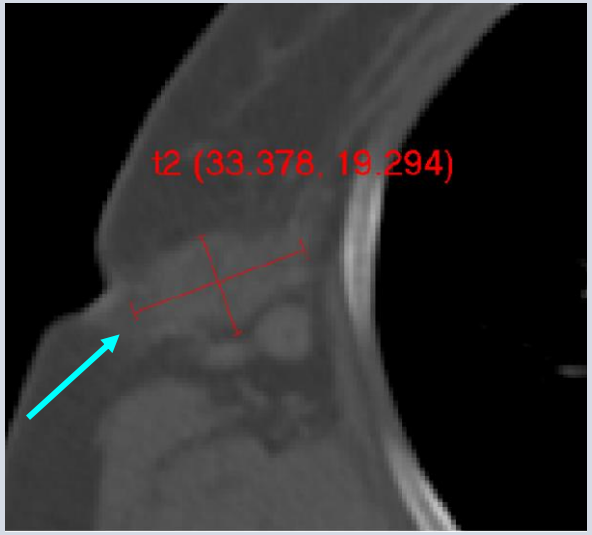
Erythroderma

*Kim et al. J Clin Invest 2005*

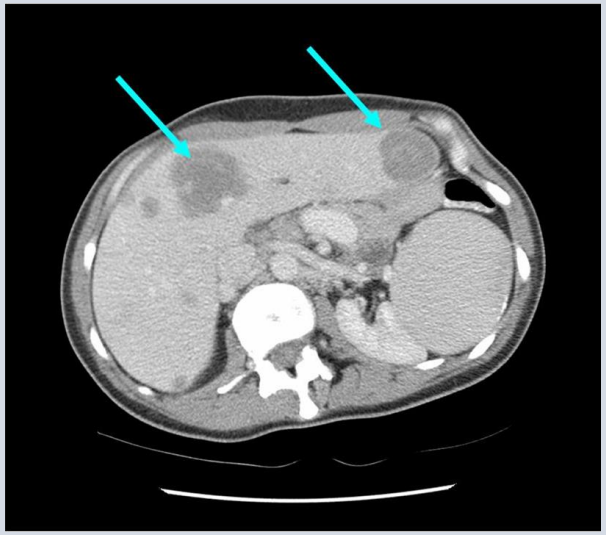
# Cutaneous T-Cell Lymphoma: Extracutaneous Manifestations



Blood (Sézary cell)




Lymph node



Viscera

# Cutaneous T-cell Lymphoma
## *ISCL/EORTC Updated Staging System*

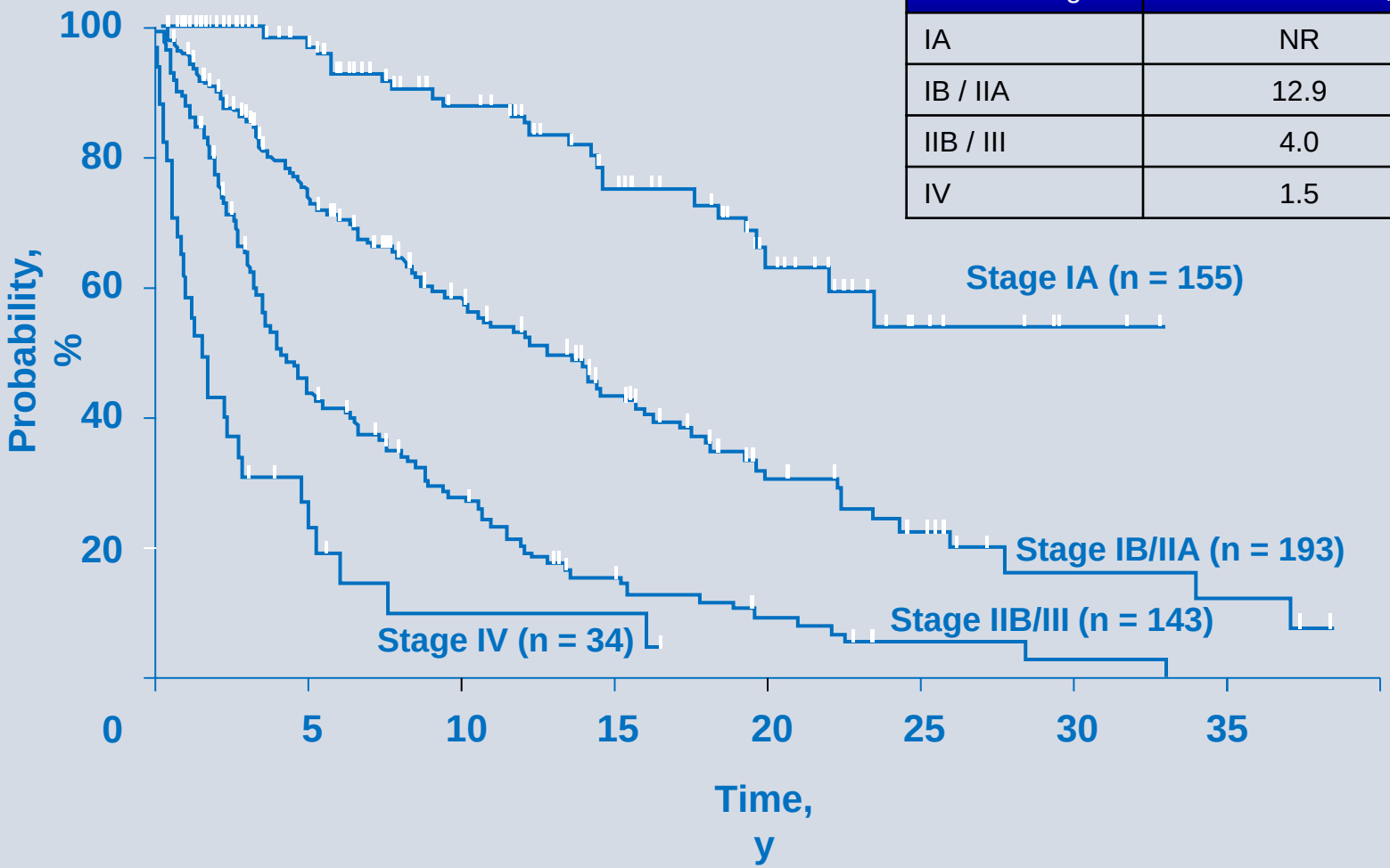
| Clinical Stage | T | N | M | B |
|---|---|---|---|---|
| IA | 1 | 0 | 0 | 0,1 |
| IB | 2 | 0 | 0 | 0,1 |
| II | 1,2 | 1,2 | 0 | 0,1 |
| IIB | 3 | 0-2 | 0 | 0,1 |
| III | 4 | 0-2 | 0 | 0,1 |
| IIIA | 4 | 0-2 | 0 | 0 |
| IIIB | 4 | 0-2 | 0 | 1 |
| $IVA_1$ | 1-4 | 0-2 | 0 | 2 |
| $IVA_2$ | 1-4 | 3 | 0 | 0-2 |
| IVB | 1-4 | 0-3 | 1 | 0-2 |

EORTC: European Organization of Research and Treatment of Cancer
ISCL: International Society for Cutaneous Lymphomas

*Olsen et al. Blood 2007*

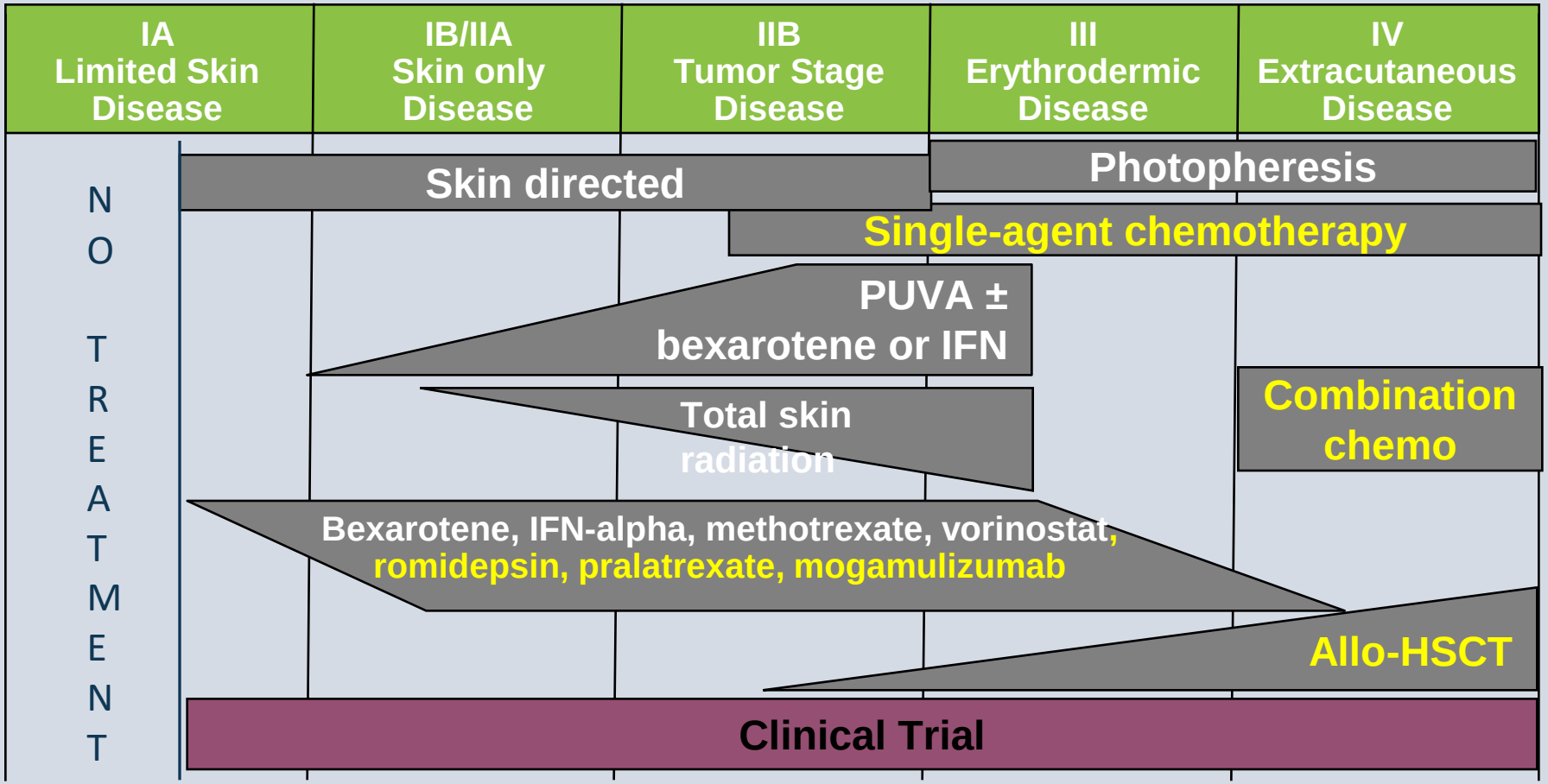
# Overall Survival by Clinical Stage

| Clinical Stage | Median Survival, y | 5-yr OS,% |
|---|---|---|
| IA | NR | 96 |
| IB / IIA | 12.9 | 73 |
| IIB / III | 4.0 | 44 |
| IV | 1.5 | 27 |




*Kim et al. Arch Dermatol 2003.*

# CTCL: NCCN Practice Guidelines




*NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas. V1.2018*

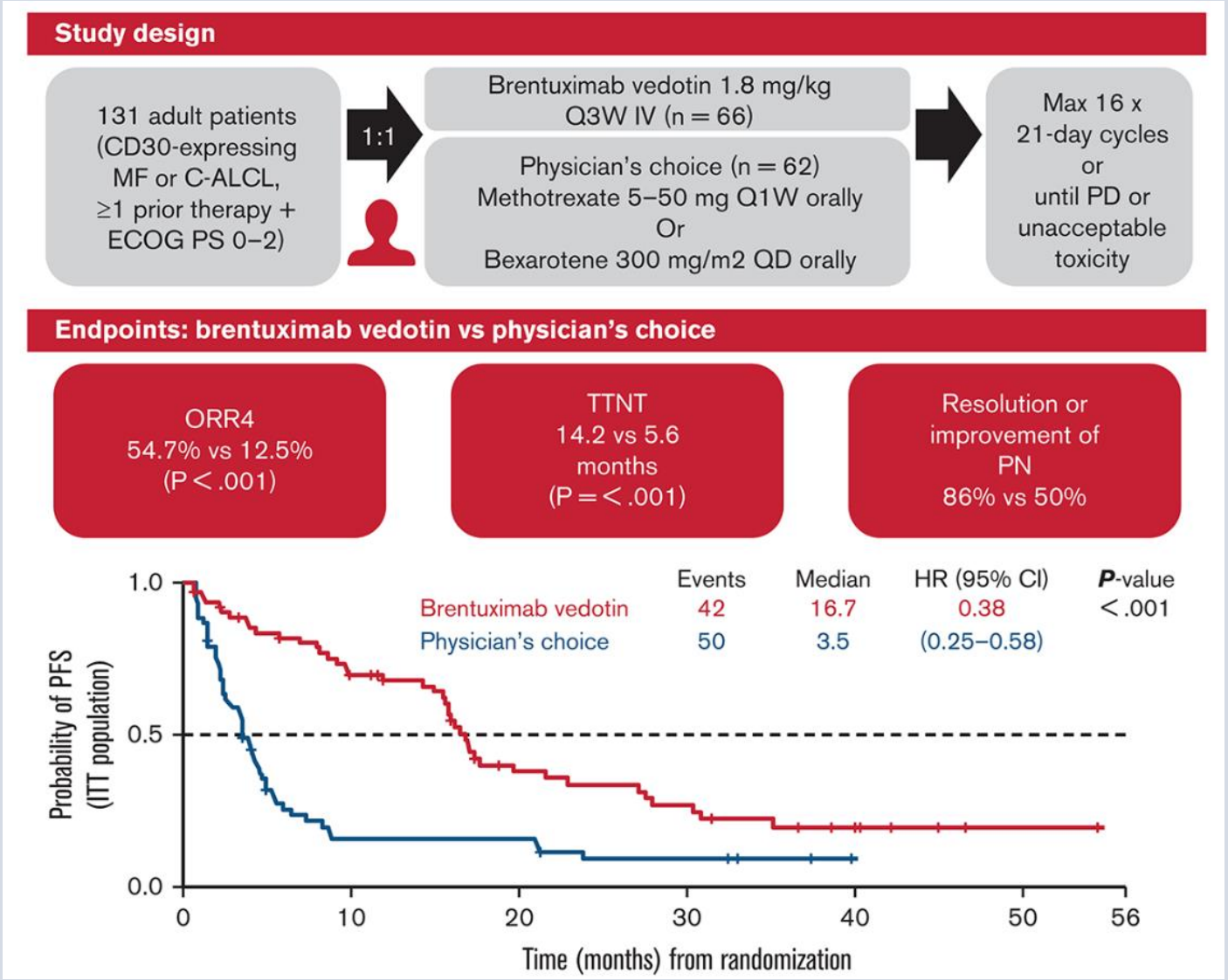
# Agents in CTCL

| Agent (Class) | Indication | N | Stage | ORR | Median DOR |
|---|---|---|---|---|---|
| Bexarotene<br>(Retinoid x-receptor activator)<br>*Miller et al. 1997* | CTCL | 52 | IIB-IVB | 32% | 5 months |
| Methotrexate<br>(dihydrofolate reductase inhibitor)<br>*Zackheim et al. 1996* | CTCL | 29 | III-IV | 58% | 31 months |
| Romidepsin<br>(HDAC inhibitor)<br>*Piekarz et al. 2009* | CTCL | 71 | IIB-IV | 34% | 13.7 months |
| Mogamulizumab<br>(CCR4 inhibitor)<br>*Kim et al. 2018* | CTCL | 372 | IB-IVB | 24% | 7.7 months |
| Brentuximab Vedotin<br>(CD30-directed ADC)<br>*Horwitz et al. 2021* | CD30+ MF, pcALCL | 128 | IB-IVB | 54.7% | 16.7 months |

# Agents in CTCL

| Agent (Class) | Study | N | Stage | ORR | Median DOR |
|---|---|---|---|---|---|
| Pralatrexate<br>(Folate analogue)<br>*Horwitz et al. 2012* | Phase I-II | 54 | IB-IVA | 45% | NR |
| Liposomal doxorubicin<br>(Anthracycline)<br>*Dummer et al. 2012* | Phase II | 49 | IIB-IVB | 41% | 6 months |
| Gemcitabine<br>(Anti-metabolite)<br>*Zinzani et al. 2000* | Phase II | 44 | IIB-IVB | 70% | 12 months |

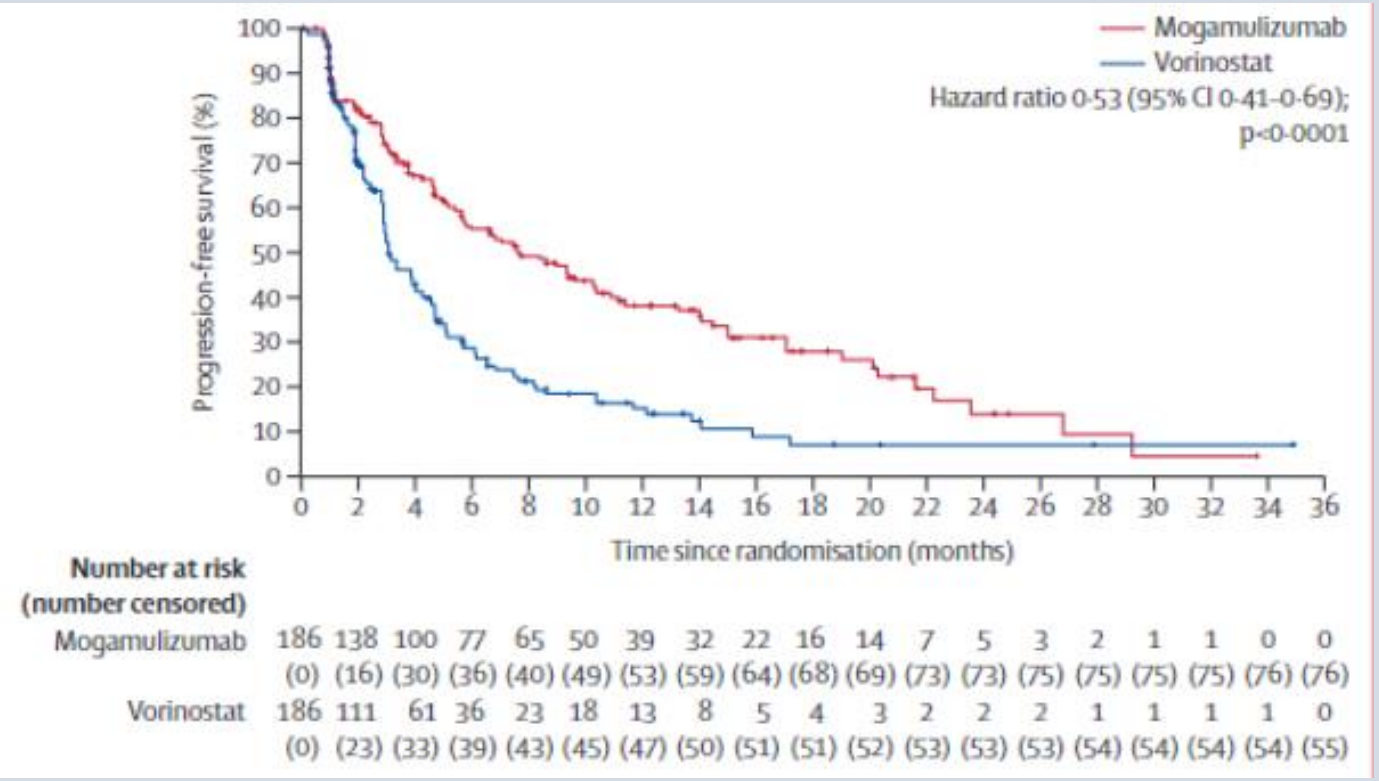
# Phase III Randomized Trial of Brentuximab Vedotin vs. Physician's Choice in Cutaneous CD30+ T-Cell Lymphoma (ALCANZA)




*Horwitz et al. Blood Adv 2021*

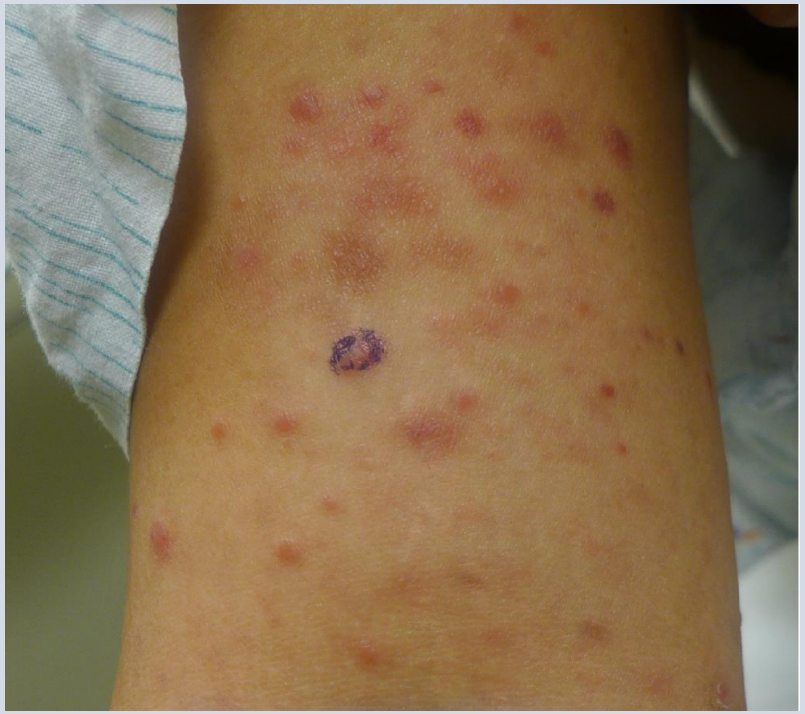
# Phase III Randomized Trial of Mogamulizumab vs. Vorinostat in Previously Treated Cutaneous T-cell Lymphoma (MAVORIC)

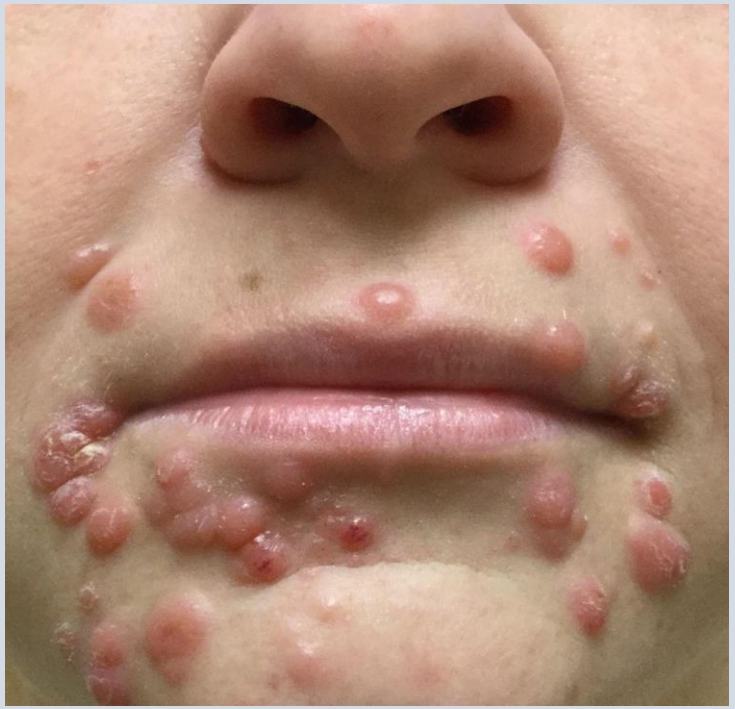
- Dx: stage IB-IVB MF or SS
- ≥ 1 prior systemic therapy failure
- Treatment regimen: Mogamulizumab 1 mg/kg IV QW -> Q2W; Vorinostat 400 mg PO QD; crossover allowed.
- Primary endpoint: PFS per investigator
- Median PFS: 7.7 with mogamulizumab vs 3.1 months

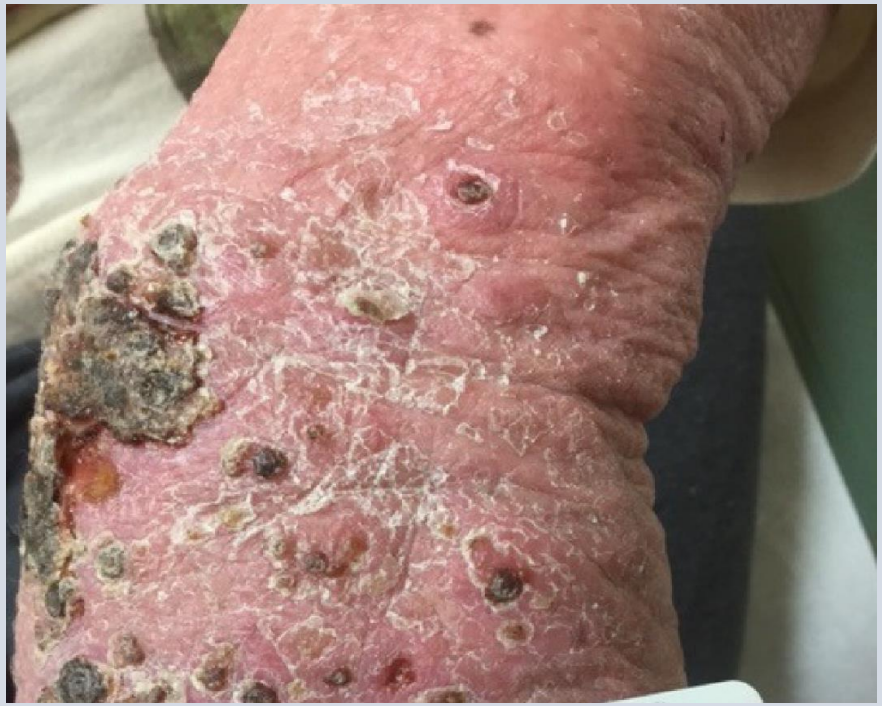



*Kim et al. Lancet Oncol 2018*

# Non-MF types of CTCL: Lymphomatoid Papulosis (LyP)

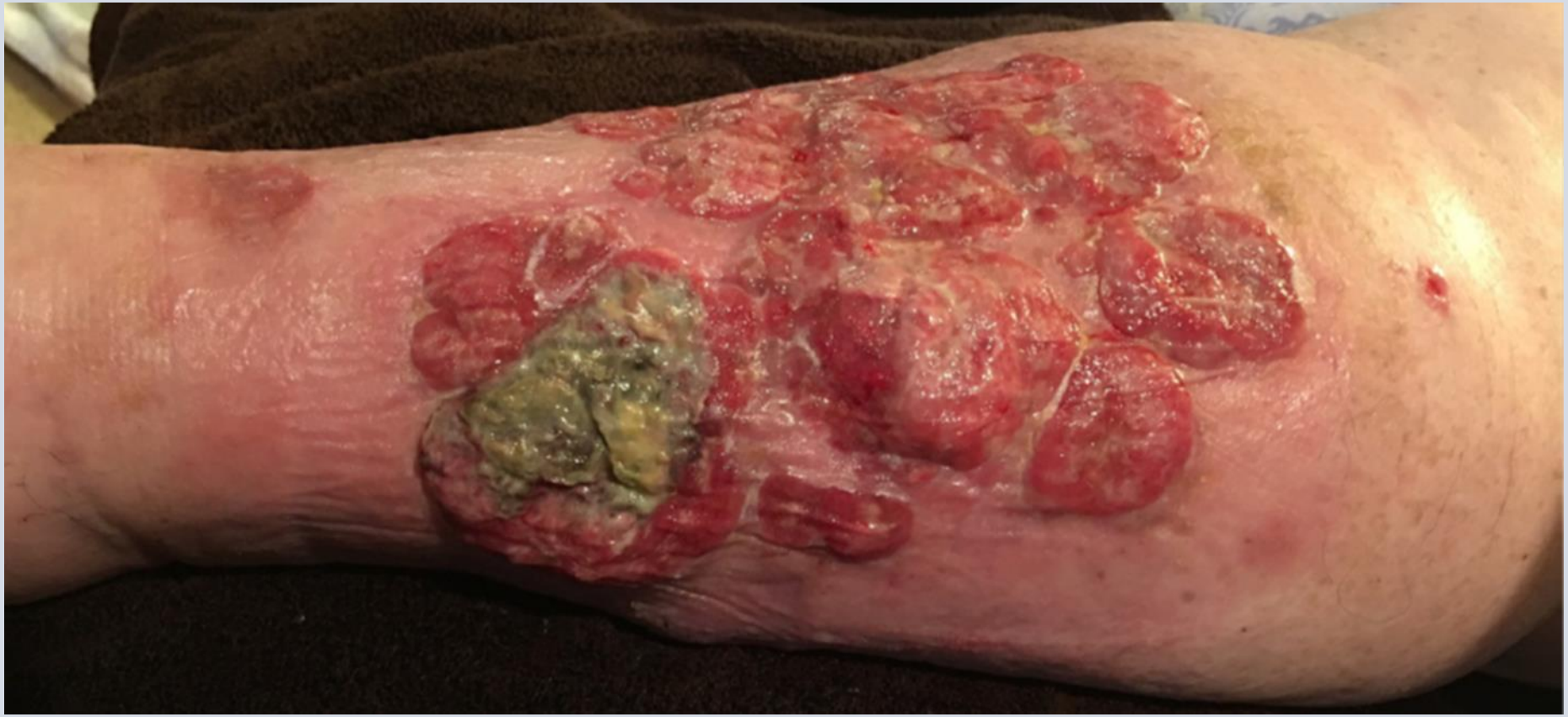






- Learning points:
  - **Asymptomatic: OBSERVE!**
  - Symptomatic, limited lesions: topical steroids or phototherapy (NB-UVB)
  - Symptomatic, extensive lesions: **methotrexate**, phototherapy

# Non-MF types of CTCL: Primary Cutaneous ALCL



- Learning points:
  - Solitary/grouped lesions: **ISRT**
  - Multifocal: **brentuximab**, methotrexate, observation of asymptomatic

# Summary

- Management is complicated by involvement of multiple specialists with different areas of expertise: pathology, dermatology, medical oncology
- Early stage usually involves skin-directed treatments
- Advanced stage usually involves systemic treatments
  - ALCANZA: brentuximab is superior to physician’s choice therapy for CD30+ mycosis fungoides and cALCL
  - MAVORIC: mogamulizumab superior to physicians’ choice therapy for mycosis fungoides and sezary syndrome

# Supportive Care Points

- Brentuximab
  - Progressive multifocal leukoencephalopathy (PML) caused by JC Virus reactivation
- Alemtuzumab
  - CMV reactivation, bone marrow suppression, infusion reactions (rigors, fevers)
- Pralatrexate
  - Mucositis: prophylaxis with vitamin B12, folate and oral leucovorin
- Mogamulizumab
  - Rash: can mimic cutaneous TCL; biopsy is essential to differentiate
  - Risk of GVHD in those heading to allogeneic SCT within 50 days of mogamulizumab
- Tumor flare reaction with lenalidomide
  - Painful lymph node enlargement +/- splenomegaly, fever, rash; with treatment initiation
  - Steroids + supportive care


Thank You